STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 150423

TO: Shaojia A Jiang
Location: REM 4B09
Art Unit: 1617
April 11, 2005

Case Serial Number: 10/627160

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 11:24:08 ON 11 APR 2005
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FILE COVERS 1907 - 11 Apr 2005  VOL 142 ISS 16
FILE LAST UPDATED: 10 Apr 2005  (20050410/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L1              STR
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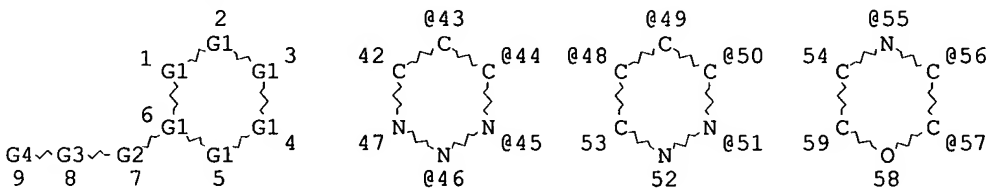

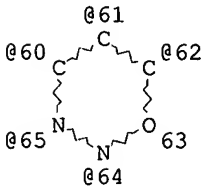


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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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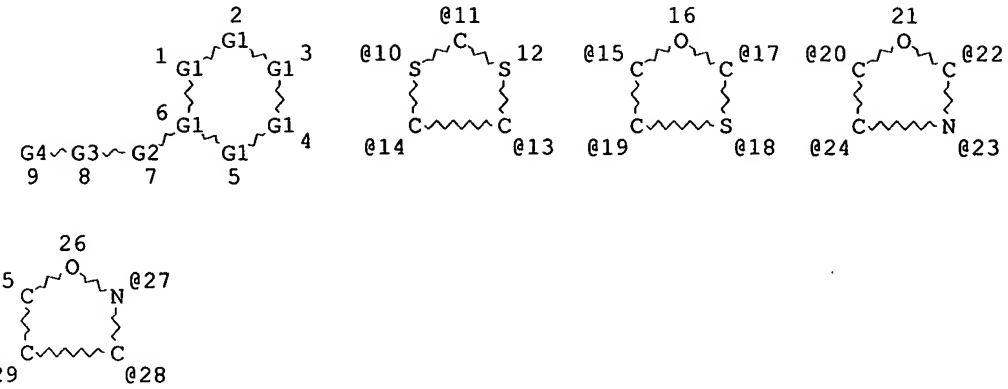

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STEREO ATTRIBUTES: NONE
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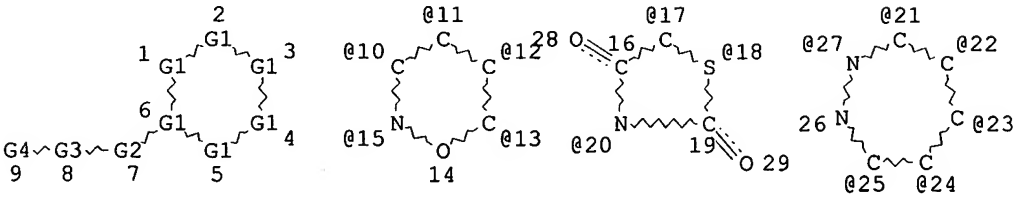

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STEREO ATTRIBUTES: NONE
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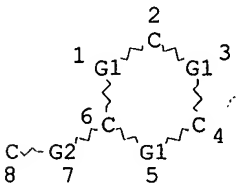

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
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STEREO ATTRIBUTES: NONE
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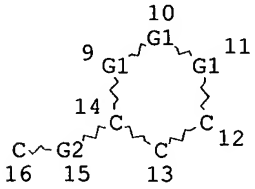

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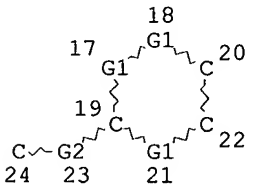

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RING(S) ARE ISOLATED OR EMBEDDED
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STEREO ATTRIBUTES: NONE
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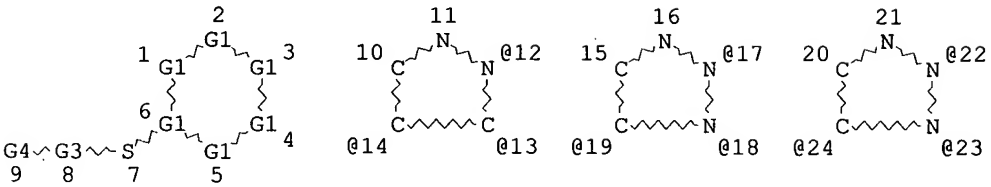

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DEFAULT MLEVEL IS ATOM
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STEREO ATTRIBUTES: NONE
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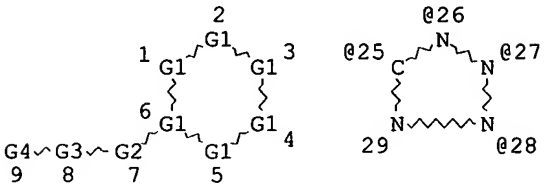

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
L42 STR

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VAR G2=O/S
REP G3=(1-15) C
VAR G4=31/33/34/35
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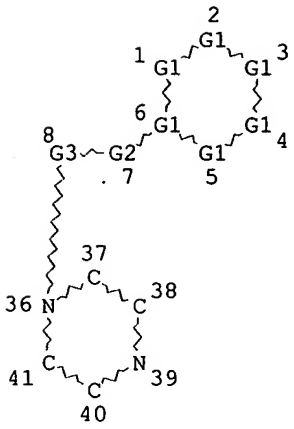
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 30
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L46 STR



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VAR G2=O/S
REP G3=(1-15) C
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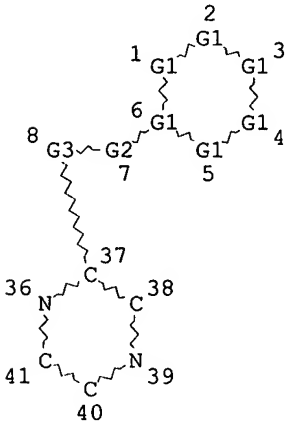
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 36
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
L51 STR



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VAR G2=O/S
REP G3=(1-15) C
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 36
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
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L56 24803 SEA FILE=REGISTRY SSS FUL L4 AND (L8 OR L9 OR L10)

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L59         2611 SEA FILE=REGISTRY SSS FUL L30 AND (L8 OR L9 OR L10)
L60         2264 SEA FILE=REGISTRY SSS FUL L37 AND (L8 OR L9 OR L10)
L61          364 SEA FILE=REGISTRY SSS FUL L42 AND (L8 OR L9 OR L10)
L62        37956 SEA FILE=REGISTRY SSS FUL L46 AND (L8 OR L9 OR L10)
L63          969 SEA FILE=REGISTRY SSS FUL L51 AND (L8 OR L9 OR L10)
L64        92378 SEA FILE=REGISTRY ABB=ON  PLU=ON  L55 OR L56 OR L57 OR L59 OR
                 L60 OR L61 OR L62 OR L63
L65        14878 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L64
L66           62 SEA FILE=REGISTRY ABB=ON  PLU=ON  (PPARΓ/BI OR PPAR.GAMMA
                 .1/BI OR PPARΓ2/BI OR PPARΓ4/BI OR PPARΓE1/BI
                  OR PPARΓFS/BI)
L67          252 SEA FILE=REGISTRY ABB=ON  PLU=ON  PEROXISOME(L)PROLIFER?(L)RECE
                 PT?(L)GAMMA
L68          116 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L66 OR L67
L69         5023 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (PEROXISOME(W)PROLIFER?(W)ACTI
                 VAT?(5A)RECEPT? OR PPAR)(L)GAMMA
L70          235 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L68 OR L69) AND L65
L71          888 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L65(L)(?NEOPLAS? OR ?CANCER?
                 OR ?TUMOR? OR ?LEUKEM?)
L72           14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L71 AND L70


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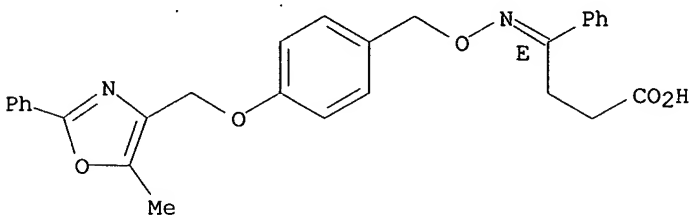
=> d ibib abs hitstr l72 1-14

L72  ANSWER 1 OF 14  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:283359  HCAPLUS
TITLE:                   Medicinal composition
INVENTOR(S):             Kawasugi, Kaname
PATENT ASSIGNEE(S):      Japan
SOURCE:                  PCT Int. Appl., 14 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                Japanese
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
     ---------------      ----   --------    -------------------    --------
     WO 2005027967         A1    20050331    WO 2003-JP11847        20030917
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       WO 2003-JP11847        20030917
AB   A medicinal composition which contains an insulin resistance-improving drug and
     vitamin B1 or its derivative  In this medicinal composition, the side effects of
     the insulin resistance-improving drug of inducing edema, heart
     enlargement, anemia, etc. are prevented by using vitamin B1 or its derivative
     together.  It is usable as a remedy for diabetes, a remedy for
     lifestyle-related diseases, an antitumor agent, an antirheumatoid drug and
     so on.
IT   250601-04-8, TAK 559
     RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (PPARγ agonist insulin resistance-improving
        drugs and vitamin B1 or its derivs. as remedies for lifestyle-related
```

diseases, **antitumor** agents, antirheumatoid drugs, etc.)
RN 250601-04-8 HCAPLUS
CN Benzenebutanoic acid, γ-[[[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]imino]-, (γE)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L72 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:216621 HCAPLUS
DOCUMENT NUMBER: 142:291341
TITLE: Composition and method for the treatment of cancer and other physiologic conditions based on modulation of the **PPAR-γ** pathway and the HER kinase axis
INVENTOR(S): Agus, David B.; Jain, Anjali; Hedvat, Michael
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005020923	A2	20050310	WO 2004-US28071	20040827

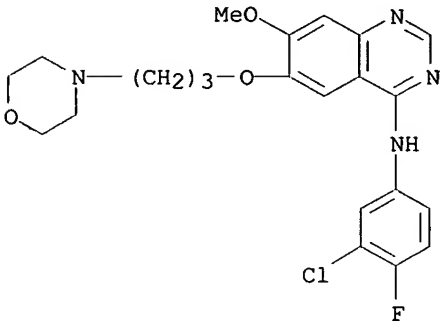
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-498849P P 20030829
US 2004-568910P P 20040507

AB Methods are described for using a NSAID and a HER kinase axis inhibitor for the treatment of various conditions including cancer, and especially prostate, breast, lung, ovarian, brain and colon cancers, through regulation of **PPARγ** activity. In various embodiments, the NSAID and HER kinase axis inhibitor may be included in a composition that is useful for the treatment of conditions in a mammal. Also described is a kit including a NSAID and a HER kinase axis inhibitor along with instructions for use in treating and preventing disease conditions, e.g. cancer.

IT **184475-35-2**, Gefitinib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(composition and method for treatment of **cancer** and other conditions based on modulation of **PPAR-γ** pathway and HER kinase axis)

RN 184475-35-2 HCAPLUS
CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



L72 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:964997 HCAPLUS
DOCUMENT NUMBER: 141:410816
TITLE: Preparation of azaheterocyclyl-substituted diphenylpyridines as Akt inhibitors for the treatment of cancer
INVENTOR(S): Bilodeau, Mark T.; Duggan, Mark E.; Hartnett, John C.; Lindsley, Craig W.; Wu, Zhicai; Zhao, Zhijian
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004096131	A2	20041111	WO 2004-US12188	20040420

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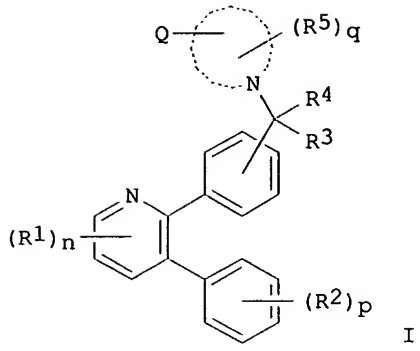
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-465260P P 20030424
OTHER SOURCE(S): MARPAT 141:410816
GI



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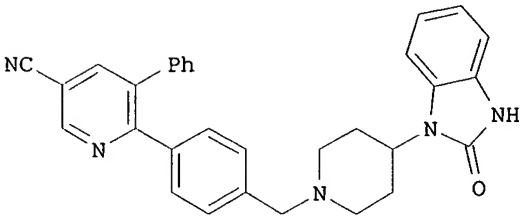


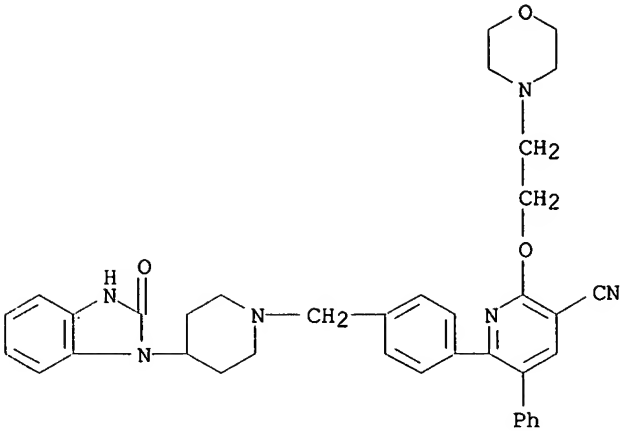
II

AB Azaheterocyclyl-substituted diphenylpyridines I [uppermost nitrogen-containing ring is a heterocycle; R1, R2, R5 = (un)substituted alkyl, aryl, heteroaryl, alkenyl, alkynyl, HO2C, NC, halo, HO, OHC, O2N, alkoxy, etc.; R3, R4 = H, alkyl, perfluoroalkyl; R3, R4, and the carbon to which they are bonded may form a carbocycle or a heterocycle containing O, S, S(:O), SO2, (un)substituted N or NHC(:O); n = 0-3; p = 0-2; q = 0-3] such as II are prepared as inhibitors of Akt1, Akt2, or Akt3 for the treatment of cancer alone or in conjunction with other drugs or radiation therapy. Trifluorosulfonylation of 6-hydroxy-5-phenyl-3-pyridinecarbonitrile, palladium-catalyzed Suzuki coupling with 4-formylphenylboronic acid, and reductive amination of the aldehyde with 1-(4-piperidinyl)-2,3-dihydro-2-benzimidazolone yields II as its TFA salt. I inhibit one or more of Akt1, Akt2, or Akt3 with IC50 values of ≤ 50 μM (no data).

IT **791851-43-9P 791852-14-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(invention compound; preparation of azaheterocyclyl-substituted diphenylpyridines as Akt inhibitors for the treatment of **cancer**)

RN 791851-43-9 HCAPLUS

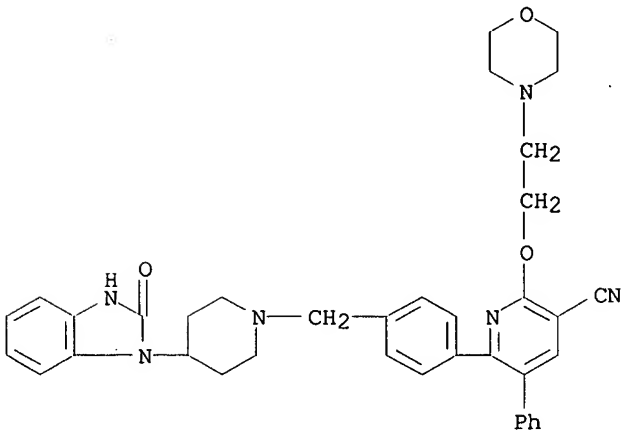
CN 3-Pyridinecarbonitrile, 6-[4-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]methyl]phenyl]-2-[2-(4-morpholinyl)ethoxy]-5-phenyl- (9CI) (CA INDEX NAME)



RN 791852-14-7 HCAPLUS
CN 3-Pyridinecarbonitrile, 6-[4-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]methyl]phenyl]-2-[2-(4-morpholinyl)ethoxy]-5-phenyl-, trifluoroacetate (9CI) (CA INDEX NAME)

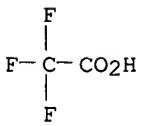
CM 1

CRN 791851-43-9
CMF C37 H38 N6 O3



CM 2

CRN 76-05-1
CMF C2 H F3 O2



L72 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:433750 HCAPLUS
DOCUMENT NUMBER: 141:7131
TITLE: Preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for the treatment of cancer
INVENTOR(S): Barnett, Stanley F.; Defeo-Jones, Deborah D.; Hartman, George D.; Huber, Hans E.; Stirdivant, Steven M.; Heimbrook, David C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 121 pp., which
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004102360	A1	20040527	US 2003-678565		20031003
PRIORITY APPLN. INFO.:			US 2002-422312P	P	20021030
			US 2003-460911P	P	20030407

OTHER SOURCE(S): MARPAT 141:7131
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

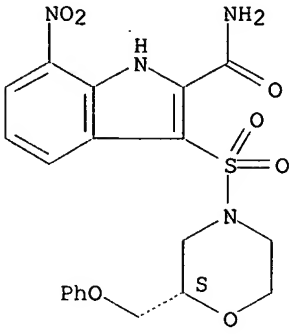
AB The present invention relates to methods of treating cancer using a combination of at least two Akt inhibitors I [wherein Q = (un)substituted heterocyclyl, aryl; U, V, W, and X = independently CH, N; Y, Z = independently CH, N, provided that at least one of Y and Z = N; n = 0-3; p = 0-2; q = 0-4; R1, R2, R7 = independently halo, CN, OH, CHO, NO2, or (un)substituted (cyclo)alkyl(oxy), alkenyl(oxy), alkynyl(oxy), heterocyclyl(oxy), acyl, carboxy, carbamoyl(oxy), ureido, sulfamoyl, etc.; R3, R4 = independently H, (perfluoro)alkyl; or CR3R4 = cycloalkyl, heterocyclyl; and pharmaceutically acceptable salts or stereoisomers thereof] or a combination of I and a protein kinase inhibitor II [wherein G = H2, O; X = C, N, SO0-2, O; m = 0-2; n = 0-2; p = 0-6; q = 0-4; R1 = independently H, halo, or (un)substituted (cyclo)alkyl, heterocyclyl, aryl, carbamoyl, amino, acyl, sulfamoyl, carboxy, etc.; R2 = H or (un)substituted (cyclo)alkyl(oxy), amino, aryloxy, heterocyclyloxy, alkenyloxy, alkynyloxy, etc.; R5 = independently H, halo, NO2, CN, or (un)substituted alkyl, alkenyl, alkynyl, carboxy, acyl, sulfamoyl, carbamoyl, ureido, amino, etc.; and pharmaceutically acceptable salts or stereoisomers thereof], optionally in combination with a third compound Examples include syntheses for I and II and assays demonstrating Akt inhibitor activity, antitumor activity, and the synergistic effect of combinations of AKT inhibitors and/or protein kinase inhibitors on caspase 3 activity. For instance, III•HCl was prepared in an 8-step reaction sequence culminating with the cycloaddn. of 4-(2-aminoprop-2-yl)benzil and o-phenylenediamine using glacial acetic acid in H2O, followed by work up with chloroform and ethanolic HCl. III•HCl, a selective Akt1 and Akt2 inhibitor, demonstrated a 3.2-fold in caspase 3 activation over control compared to a 1.2-fold increase for a protein kinase inhibitor. Combination treatment produced a 9-fold increase in caspase 3 activation.

IT **661468-61-7P 661468-63-9P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**antitumor** agent; preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of **cancer**)

RN 661468-61-7 HCAPLUS

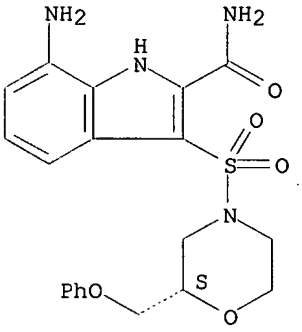
CN 1H-Indole-2-carboxamide, 7-nitro-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



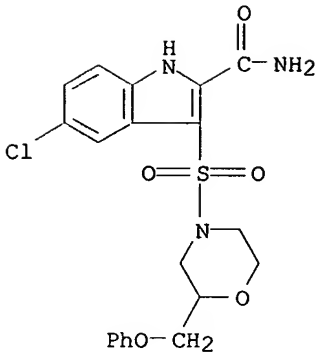
RN 661468-63-9 HCAPLUS
CN 1H-Indole-2-carboxamide, 7-amino-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



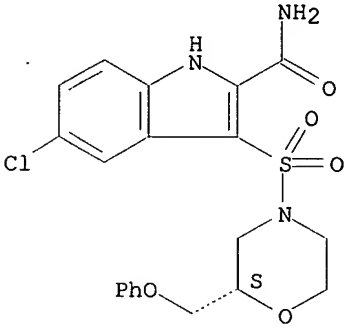
IT **661467-97-6P 661467-98-7P 661467-99-8P**
661468-12-8P 661468-13-9P 661468-14-0P
661468-53-7P 661468-54-8P 661468-55-9P
661468-65-1P 661468-67-3P 661468-75-3P
661468-76-4P 661468-87-7P 661469-61-0P
661469-89-2P 661470-00-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**antitumor** agent; preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of **cancer**)

RN 661467-97-6 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



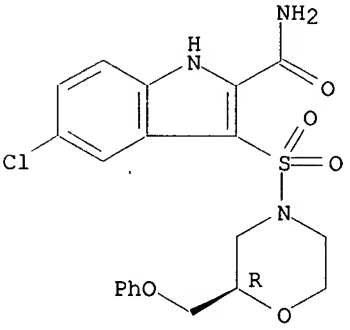
RN 661467-98-7 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-chloro-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

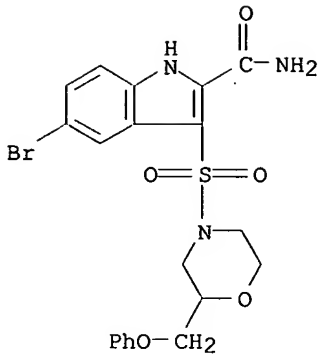


RN 661467-99-8 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-chloro-3-[[(2R)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

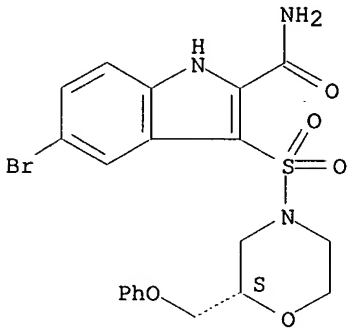


RN 661468-12-8 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-bromo-3-[[2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



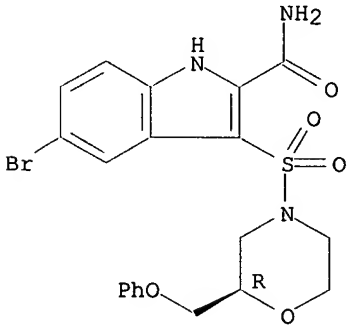
RN 661468-13-9 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-bromo-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

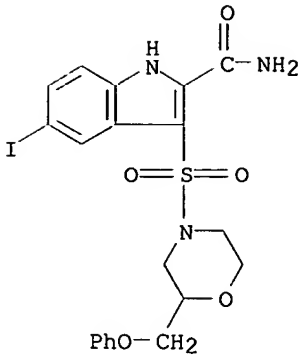


RN 661468-14-0 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-bromo-3-[[(2R)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

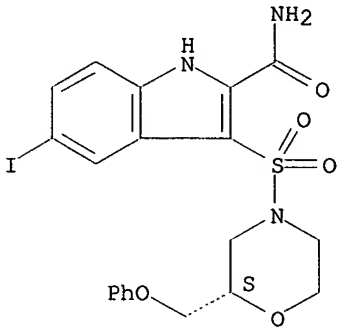


RN 661468-53-7 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-iodo-3-[[2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



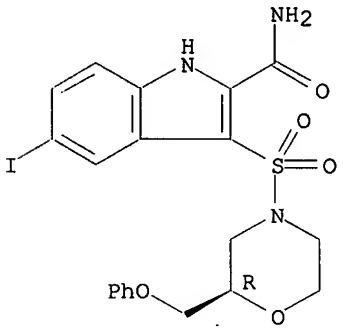
RN 661468-54-8 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-iodo-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



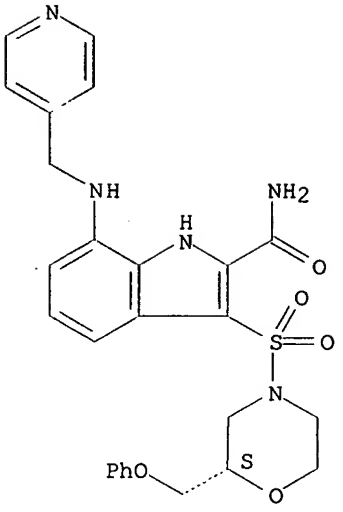
RN 661468-55-9 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-iodo-3-[[(2R)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



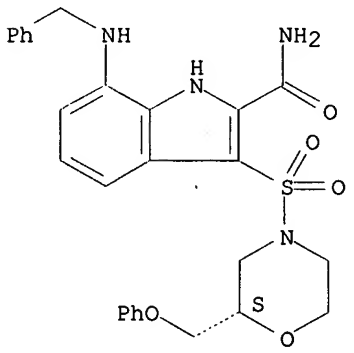
RN 661468-65-1 HCAPLUS
CN 1H-Indole-2-carboxamide, 3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-7-[(4-pyridinylmethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



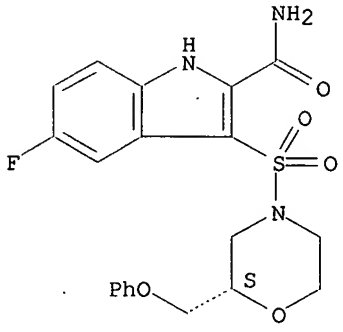
RN 661468-67-3 HCAPLUS
CN 1H-Indole-2-carboxamide, 3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-7-[(phenylmethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



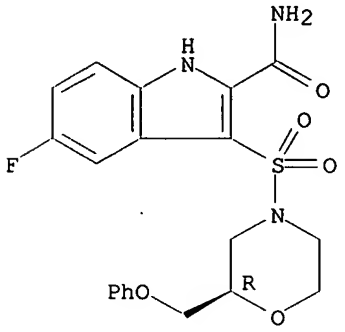
RN 661468-75-3 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-fluoro-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



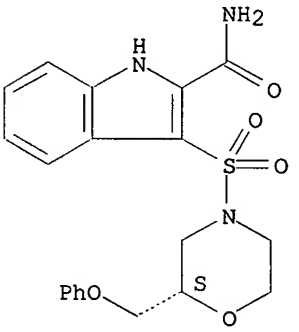
RN 661468-76-4 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-fluoro-3-[[(2R)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

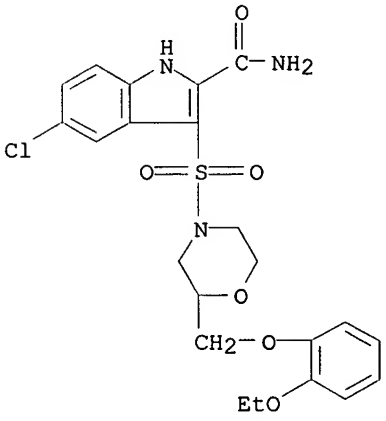


RN 661468-87-7 HCAPLUS
CN 1H-Indole-2-carboxamide, 3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

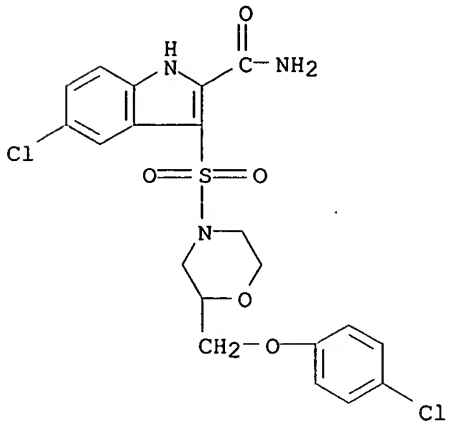


RN 661469-61-0 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-[(2-ethoxyphenoxy)methyl]-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

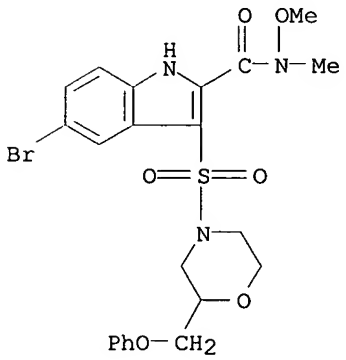


RN 661469-89-2 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-[(4-chlorophenoxy)methyl]-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



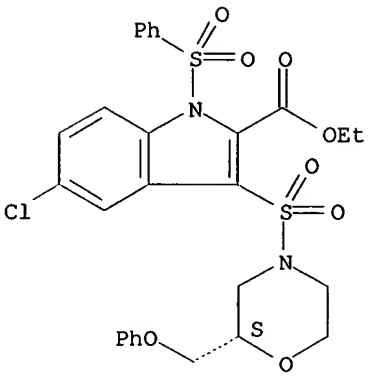
RN 661470-00-4 HCAPLUS
CN 1H-Indole-2-carboxamide, 5-bromo-N-methoxy-N-methyl-3-[[2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



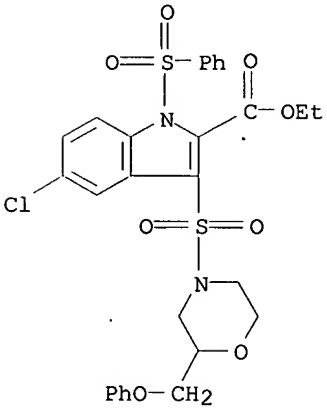
IT **661470-45-7P 695816-07-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of **cancer**)

RN 661470-45-7 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-chloro-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

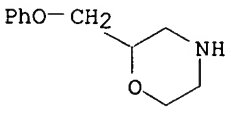
Absolute stereochemistry.



RN 695816-07-0 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-chloro-3-[[2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

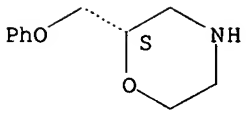


IT **167273-56-5**, 2-(Phenoxymethyl)morpholine **661470-52-6** **695816-08-1** **695816-09-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of **cancer**)
RN 167273-56-5 HCAPLUS
CN Morpholine, 2-(phenoxymethyl)- (9CI) (CA INDEX NAME)



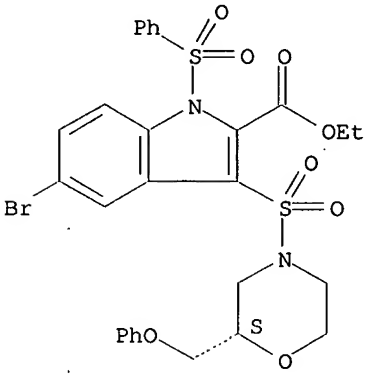
RN 661470-52-6 HCAPLUS
CN Morpholine, 2-(phenoxymethyl)-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



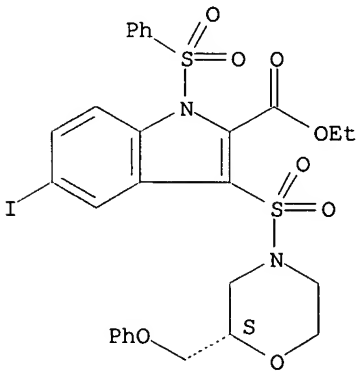
RN 695816-08-1 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-bromo-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 695816-09-2 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-iodo-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

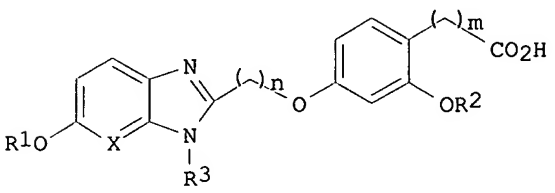


L72 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:120834 HCAPLUS
DOCUMENT NUMBER: 140:181466
TITLE: Preparation of resorcinol derivatives as **peroxisome proliferator-activated receptor (PPAR)** γ -agonists
INVENTOR(S): Shibata, Tomoyuki; Wada, Kunio; Nakamura, Yuji; Araki, Kazushi
PATENT ASSIGNEE(S): Sankyo Company, Limited, Japan

SOURCE: PCT Int. Appl., 261 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004013109	A1	20040212	WO 2003-JP9834	20030801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004123711	A2	20040422	JP 2003-205222	20030801

PRIORITY APPLN. INFO.: JP 2002-225980 A 20020802
OTHER SOURCE(S): MARPAT 140:181466
GI



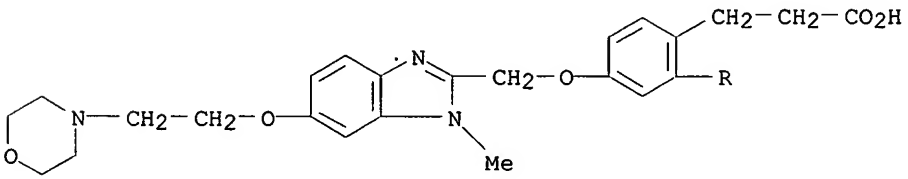
I

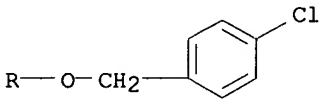
AB 4-[(Pyrido[2,3-d]imidazol-2-yl or benzimidazol-2-ylalkoxy)phenyl]propanoic acid or acetic acid derivs. represented by the following general formula (I) [wherein X = CH, N; R1 = each (un)substituted C1-6 alkyl, C3-10 cycloalkyl, C2-6 alkenyl, C6-10 aryl, C7-16 aralkyl, 4- to 10-membered heterocycle containing one to three heteroatoms selected from N, O, and S atoms; R2 = each (un)substituted C7-16 aralkyl, C9-16 aralkenyl, or alkyl substituted by a 5- to 10-membered heteroarom. ring containing one to three heteroatoms selected from N, O, and S atoms; R3 = H, C1-6 alkyl, (un)substituted C6-10 aryl; m = 1, 2; n = an integer of 1-3] or pharmacol. acceptable salts or esters thereof are prepared Also disclosed are pharmaceutical compns. containing the compds. I or pharmacol. acceptable salts or esters thereof as the active ingredients (1) for improving insulin-resistance, lowering blood sugar, or inhibiting the proliferation of cancer cells or (2) for the prevention and/or treatment of diabetes, impaired glucose tolerance, obesity, hyperlipemia, or diabetes complications. Thus, 1.09 g 3-(2-benzyloxy-4-hydroxyphenyl)propionic acid Et ester and 697 mg 2-hydroxymethyl-6-methoxy-1-methyl-1H-benzimidazole were dissolved in 30 mL toluene, treated with 1.13 mL tributylphosphine and 1.14 g 1,1'-(azodicarbonyl)dipiperidine and stirred at room temperature overnight to give 87% 3-[2-benzyloxy-4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)phenyl]propionic acid Et ester which (1.5 g) was stirred with a mixture of 7 mL EtOH, 7 mL THF, and 6.3 mL 1 N aqueous NaOH at room temperature overnight and stirred with 1 N aqueous HCl and EtOAc to give 45% 3-[2-benzyloxy-4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)phenyl]propionic acid (II). 3-[4-[2-[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]ethoxy]-2-(4-chlorobenzyloxy)phenyl]propionic acid hydrochloride was fed t male KK mice with a feed containing 0.01% II for 3 days to lower blood sugar level by 71%.

A capsule, a tablet, and a granule containing I were formulated.

IT **657429-91-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of resorcinol derivs. as **peroxisome proliferator-activated receptor** (**PPAR**) γ -agonists, **anticancer** agents, or treatment or prevention of diabetes, impaired glucose tolerance, obesity, or hyperlipemia)

RN 657429-91-9 HCAPLUS
CN Benzenepropanoic acid, 2-[(4-chlorophenyl)methoxy]-4-[[1-methyl-6-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl]methoxy]-, dihydrochloride (9CI) (CA INDEX NAME)

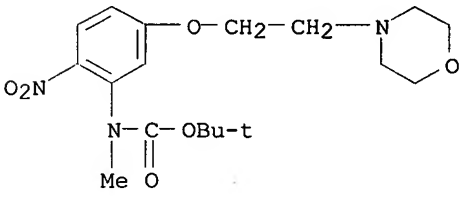




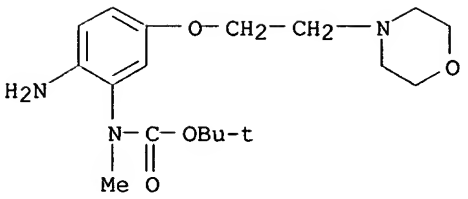
●2 HCl

IT **657431-74-8P 657431-75-9P 657431-76-0P**
657431-77-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of resorcinol derivs. as **peroxisome proliferator-activated receptor** (**PPAR**) γ -agonists, **anticancer** agents, or treatment or prevention of diabetes, impaired glucose tolerance, obesity, or hyperlipemia)

RN 657431-74-8 HCAPLUS
CN Carbamic acid, methyl[5-[2-(4-morpholinyl)ethoxy]-2-nitrophenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

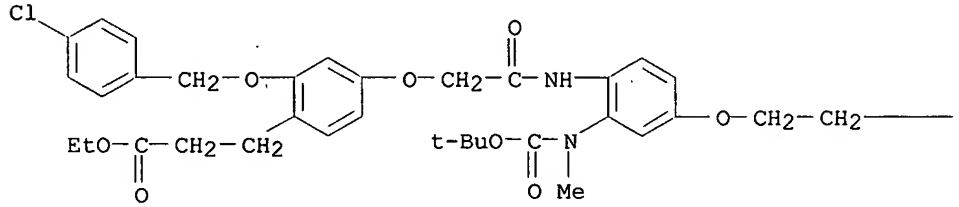


RN 657431-75-9 HCAPLUS
CN Carbamic acid, [2-amino-5-[2-(4-morpholinyl)ethoxy]phenyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

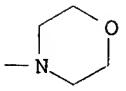


RN 657431-76-0 HCAPLUS
CN Benzenepropanoic acid, 2-[(4-chlorophenyl)methoxy]-4-[2-[[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4-[2-(4-morpholinyl)ethoxy]phenyl]amino]-2-oxoethoxy]-, ethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

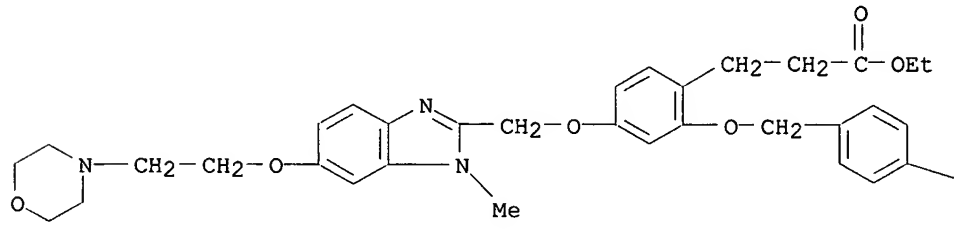


PAGE 1-B



RN 657431-77-1 HCAPLUS
CN Benzenepropanoic acid, 2-[(4-chlorophenyl)methoxy]-4-[[1-methyl-6-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl]methoxy]-, ethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



Cl

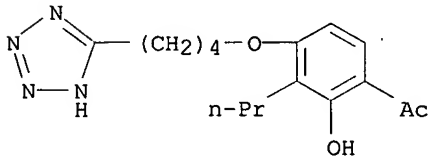
L72 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:334376 HCAPLUS
DOCUMENT NUMBER: 138:362646
TITLE: Use of lipoxygenase inhibitors and PPAR ligands as anticancer therapeutic and intervention agents
INVENTOR(S): Mulshine, James L.; Jett, Marti
PATENT ASSIGNEE(S): The United States of America as Represented by the Department of Health and Human Services, USA; The United States of America as Represented by the Secretary of the Army
SOURCE: U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003082108	A1	20030501	US 2002-186070	20020628
US 6756399	B2	20040629		
PRIORITY APPLN. INFO.:			US 2001-302155P P	20010629

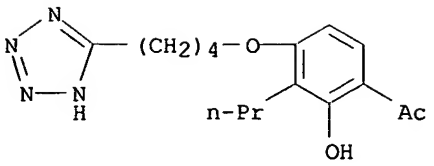
AB The invention provides a method for treating and preventing an epithelial cell-derived cancer in a subject in need thereof, comprising administering to the subject an amount of a 5-lipoxygenase inhibitor and PPAR ligand or derivs. thereof, effective to treat or prevent the epithelial cell-derived cancer. Also encompassed by the invention are inhibitors of enzymes that metabolize arachidonic acid.

IT **88107-10-2**, LY171883 **88107-10-2D**, LY171883, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipoxygenase inhibitors and PPAR ligands as **anticancer** therapeutic and intervention agents)

RN 88107-10-2 HCAPLUS
CN Ethanone, 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 88107-10-2 HCAPLUS
CN Ethanone, 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:297161 HCAPLUS
DOCUMENT NUMBER: 139:148276
TITLE: **PPARγ** Ligands and ATRA Inhibit the Invasion of Human Breast Cancer Cells in vitro
AUTHOR(S): Liu, H.; Zang, C.; Fenner, M. H.; Possinger, K.; Elstner, E.
CORPORATE SOURCE: School of Medicine (Charite), Humboldt University, Berlin, Germany
SOURCE: Breast Cancer Research and Treatment (2003), 79(1), 63-74
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Invasion and metastasis are the main causes of death in breast cancer patients. Increased expression of matrix metalloproteinases (MMPs), especially gelatinases (MMP-2 and -9), has been closely associated with tumor progression. One of the nuclear hormone **receptors** (NHR), **peroxisome proliferator-activated receptor γ** (**PPARγ**), is a ligand-activated transcriptional factor that regulates cell proliferation, differentiation and apoptosis in both normal and cancer cells. Recent data indicate that **PPARγ** activation by its ligands can also lead to the inhibition of gelatinase B (MMP-9) and the blockage of migration in macrophages and muscle cells, implying the possibility that **PPARγ** ligands may possess anti-invasive activities on tumor cells. In this study, we showed that treatment of the highly aggressive human breast cancer cell line MDA-MB-231 with the synthetic **PPARγ** ligands pioglitazone (PGZ), rosiglitazone (RGZ), GW7845 or its natural ligand 15-deoxy-Δ 12, 14-prostaglandin J2(15d-PGJ2), at concns. at which no obvious cytotoxicity was observed in vitro, led to a significant inhibition of the invasive capacities of this cell line through a reconstituted basement membrane (Matrigel) in a Transwell chamber model. All-trans-retinoic acid (ATRA), a ligand for retinoic acid receptor (RAR), was also studied and showed a similar inhibitory effect on invasion. Although no change was observed in the expression of MMP-9 after challenge with **PPARγ** ligands and/or ATRA on this cell line, the natural tissue inhibitor of gelatinases, namely the tissue inhibitor of MMP 1 (TIMP-1) was upregulated by these treatments and the gelatinolytic activities of gelatinases in the conditioned media were decreased. Since MMP-2 was not detectable in the conditioned media of MDA-MB-231 cells, and the gelatinolytic activities of the conditioned media were reduced only by MMP-9 neutralizing antibodies, it is most likely that the reduction of gelatinolytic activities by **PPAR. gamma**. ligands and/or ATRA was due to the decrease of MMP-9 activities. Because MMP-9 was absolutely required in the transmigration of this cell line through Matrigel in our in vitro model as demonstrated by neutralizing antibodies against MMP-2 and -9, we concluded that down-regulation of gelatinase activities is, at least in part, responsible for the reduction of the invasive capacities of MDA-MB-231 cell line in vitro. Our results, for the first time, indicate that **PPAR.**

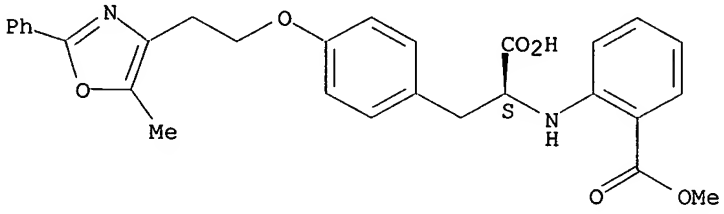
gamma. ligands may have therapeutic value for the treatment of highly invasive breast cancer by targeting its invasive behavior.

IT **196809-22-0**, GW 7845
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PPARγ** ligands and ATRA inhibit the invasion of human breast **cancer** cells in vitro)

RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

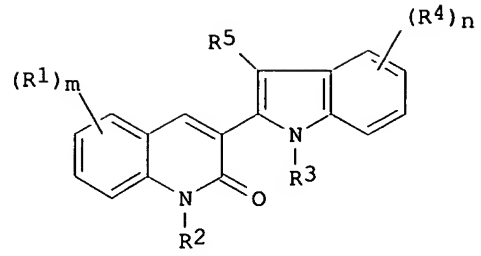


REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

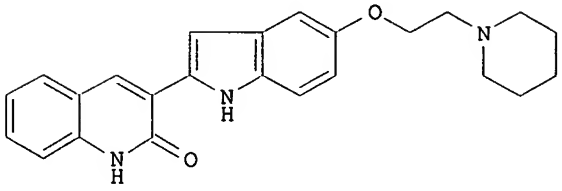
L72 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:202621 HCAPLUS
DOCUMENT NUMBER: 138:238027
TITLE: Preparation of 3-(2-indolyl)quinolin-2(1H)-ones as tyrosine kinase inhibitors
INVENTOR(S): Peckham, Jennifer P.; Hoffman, William F.; Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.; Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020699	A2	20030313	WO 2002-US27114	20020826
WO 2003020699	A3	20030522		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004235826	A1	20041125	US 2004-487589	20040224
PRIORITY APPLN. INFO.:			US 2001-316123P P	20010830
			WO 2002-US27114 W	20020826

GI



I



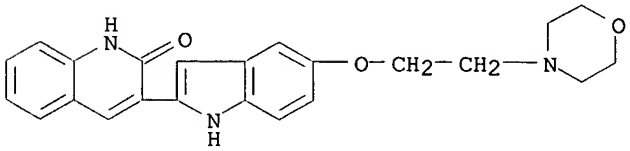
II

AB Title compds., including I (R groups undefined), were prepared and inhibitors, regulators, and/or modulators of tyrosine kinase signal transduction. For example, 1-(tert-butoxycarbonyl)-5-[(tert-butyldimethylsilyl)oxy]-1H-indol-2-ylboronic acid was coupled with 2-chloro-3-iodoquinoline (preparation of starting materials given) in the presence of Pd(PPh3)4 and K3PO4 in dioxane to give the protected 3-(2-indolyl)quinoline derivative Deprotection using triethylamine trihydrofluoride afforded the alc. Reaction with 1-(2-chloroethyl)piperidine•HCl and Cs2CO3 in DMF followed by reflux at 110° in AcOH and H2O for 12 h provided II. Compds. of the invention inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 μM - 5.0 μM. Thus, I and compns. containing I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT **335649-66-6P**, 3-[5-[2-(Morpholin-4-yl)ethoxy]-1H-indol-2-yl]-1H-quinolin-2-one **335649-74-6P**, 3-[5-[3-(Morpholin-4-yl)propoxy]-1H-indol-2-yl]-1H-quinolin-2-one **408502-03-4P**, 3-[5-[3-(4-Methylpiperazin-1-yl)propoxy]-1H-indol-2-yl]-1H-quinolin-2-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tyrosine kinase inhibitor; preparation of (indolyl)quinolinones for treatment of **cancer**, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)

RN 335649-66-6 HCAPLUS

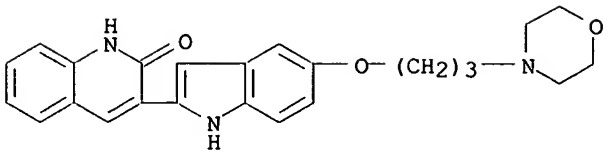
CN 2(1H)-Quinolinone, 3-[5-[2-(4-morpholinyl)ethoxy]-1H-indol-2-yl]- (9CI) (CA INDEX NAME)



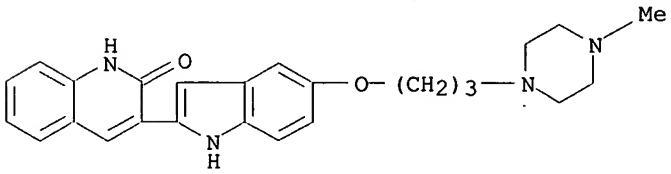
RN 335649-74-6 HCAPLUS

CN 2(1H)-Quinolinone, 3-[5-[3-(4-morpholinyl)propoxy]-1H-indol-2-yl]- (9CI)

(CA INDEX NAME)



RN 408502-03-4 HCAPLUS
CN 2(1H)-Quinolinone, 3-[5-[3-(4-methyl-1-piperazinyl)propoxy]-1H-indol-2-yl]- (9CI) (CA INDEX NAME)



L72 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:868247 HCAPLUS
DOCUMENT NUMBER: 138:148045
TITLE: 15-Deoxy-Δ12,14-prostaglandin J2-induced apoptosis does not require **PPAR**. **gamma**. in breast cancer cells
AUTHOR(S): Clay, Carl E.; Monjazeb, Arta; Thorburn, Jacqueline; Chilton, Floyd H.; High, Kevin P.
CORPORATE SOURCE: Department of Internal Medicine, Section of Pulmonary Critical Care, Wake Forest University Baptist Medical Center, Winston Salem, NC, 27157, USA
SOURCE: Journal of Lipid Research (2002), 43(11), 1818-1828
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Naturally occurring derivs. of arachidonic acid are potent agonists for the nuclear hormone **receptor peroxisome proliferator-activated receptor gamma** (**PPARγ**) and block cancer cell proliferation through the induction of apoptosis. The authors have previously reported that induction of apoptosis using cyclopentenone prostaglandins of the J series, including 15-deoxy-Δ12,14-PGJ2 (15dPGJ2), is associated with a high degree of **PPAR**-response element (PPRE) activity and requires early de novo gene expression in breast cancer cells. In the current study, the authors used pharmacol. and genetic approaches to test the hypothesis that **PPARγ** is required for 15dPGJ2-induced apoptosis. The **PPARγ** agonists 15dPGJ2, troglitazone (TGZ), and GW7845, a synthetic and highly selective tyrosine-based **PPARγ** agonist, all increased transcriptional activity of **PPARγ** , and expression of CD36, a **PPARγ** -dependent gene. Transcriptional activity and CD36 expression was reduced by GW9662, a selective and irreversible **PPARγ** antagonist, but GW9662 did not block apoptosis induced by 15dPGJ2. Moreover, dominant neg. expression of **PPARγ** blocked PPRE transcriptional activity, but did not block 15dPGJ2-induced apoptosis. These studies show that while 15dPGJ2 activates PPRE-mediated transcription, **PPARγ** is not required for 15dPGJ2-induced apoptosis in breast cancer cells. Other likely mechanisms

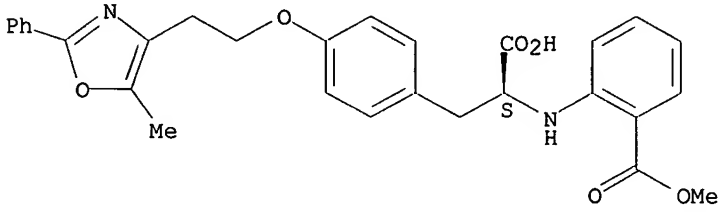
through which cyclopentenone prostaglandins induce apoptosis of cancer cells are discussed.

IT **196809-22-0**, GW 7845
RL: PAC (Pharmacological activity); BIOL (Biological study)
(**PPARγ** agonist; deoxyPGJ2 induction of apoptosis by mechanism independent of **PPARγ** in breast **cancer** cells)

RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:142553 HCAPLUS
DOCUMENT NUMBER: 136:177969
TITLE: Medicinal compositions containing **PPAR. gamma.** agonists and RXR agonists for preventing and treating cancer
INVENTOR(S): Kurakata, Shinichi; Fujiwara, Kosaku; Shimazaki, Naomi; Fujita, Takashi
PATENT ASSIGNEE(S): Sankyo Company, Ltd., Japan
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002013864	A1	20020221	WO 2001-JP7037	20010815
W: AU, BR, CA, CN, CO, CZ, HU, ID, IL, IN, KR, MX, NO, NZ, PL, RU, SG, SK, US, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
JP 2002128700	A2	20020509	JP 2001-241740	20010809
AU 2001078738	A5	20020225	AU 2001-78738	20010815
PRIORITY APPLN. INFO.:			JP 2000-246910 A	20000816
			WO 2001-JP7037 W	20010815

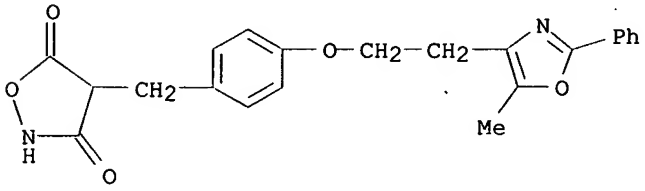
OTHER SOURCE(S): MARPAT 136:177969

AB Disclosed are medicinal compns. for preventing or treating cancer wherein one or more **Peroxisome proliferator-activated receptor γ (PPARγ)** activation agonists and one or more retinoid X receptor (RXR) activation agonists are used simultaneously or successively. A combined administration of 5-[4-(6-methoxy-1-methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione hydrochloride (I) 5 and targretin 100 mg/kg to HL-60 cell-bearing mice showed synergistic antitumor effect. Also, tablets were prepared from I 0.004, targretin 0.1, lactose 0.244, corn starch 50, and magnesium stearate 0.002 g.

IT **170861-63-9 196808-45-4**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

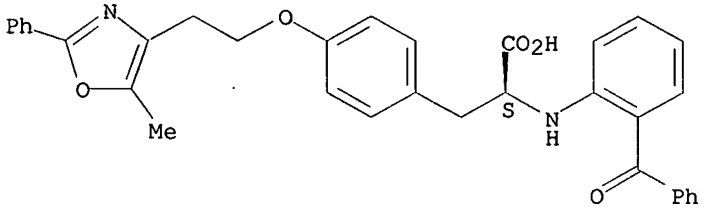
(simultaneous or successive use of **PPARγ** agonists and RXR agonists for prevention or treatment of **cancer**)

RN 170861-63-9 HCAPLUS
CN 3,5-Isoxazolidinedione, 4-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 196808-45-4 HCAPLUS
CN L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:489258 HCAPLUS
DOCUMENT NUMBER: 135:71267
TITLE: Treating cancers associated with overexpression of class I family of receptor tyrosine kinases by use of a strongly binding **PPARγ** ligand
INVENTOR(S): Dannenberg, Andrew J.; Subbaramaiah, Kotha
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

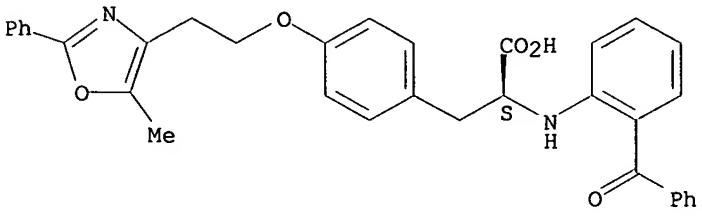
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047555	A1	20010705	WO 2000-US32442	20001211
W: CA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 6291496	B1	20010918	US 1999-472179	19991227
PRIORITY APPLN. INFO.:			US 1999-472179 A	19991227

AB Cancers associated with overexpression of class I family of receptor tyrosine kinases, e.g., with overexpression of HER-2/neu or overexpression of epidermal growth factor receptor, are treated with strongly binding **PPARγ** ligands.
IT **196808-45-4 196809-22-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**PPARγ** ligands for treatment of **cancers** associated with overexpression of class I family of receptor tyrosine kinases)

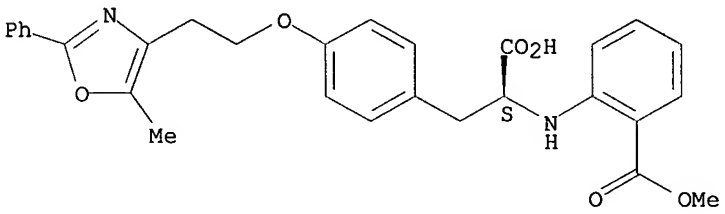
RN 196808-45-4 HCAPLUS
CN L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 196809-22-0 HCAPLUS
CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:368081 HCAPLUS
DOCUMENT NUMBER: 133:12750
TITLE: Method using a **PPARγ** ligand/agonist for inhibiting angiogenesis and treating tumor growth
INVENTOR(S): Gerritsen, Mary E.; Xin, Xiaohua E.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000030628	A2	20000602	WO 1999-US27612	19991118
WO 2000030628	A3	20011011		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2350599	AA	20000602	CA 1999-2350599	19991118
EP 1143953	A2	20011017	EP 1999-960538	19991118
EP 1143953	A3	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001036955	A1	20011101	US 2001-865859	20010525
PRIORITY APPLN. INFO.:			US 1998-109328P	P 19981120
			US 1999-116530P	P 19990120
			US 1999-443010	B1 19991117
			WO 1999-US27612	W 19991118

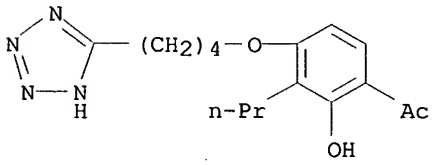
OTHER SOURCE(S): MARPAT 133:12750

AB Angiogenesis is inhibited and the growth of tumors is treated by administering an effective amount of a **PPARγ** ligand/agonist, optionally with an RXR receptor ligand.

IT **88107-10-2**, LY 171883
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**PPARγ** ligand/agonist for inhibiting angiogenesis and treating **tumor** growth)

RN 88107-10-2 HCAPLUS

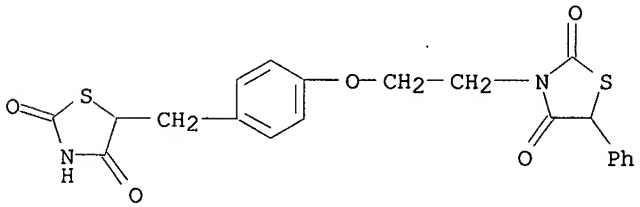
CN Ethanone, 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]- (9CI) (CA INDEX NAME)



IT **143811-62-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**PPARγ** ligand/agonist for inhibiting angiogenesis and treating **tumor** growth)

RN 143811-62-5 HCAPLUS

CN 2,4-Thiazolidinedione, 3-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy] ethyl]-5-phenyl- (9CI) (CA INDEX NAME)



L72 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:52487 HCAPLUS

DOCUMENT NUMBER: 132:202817

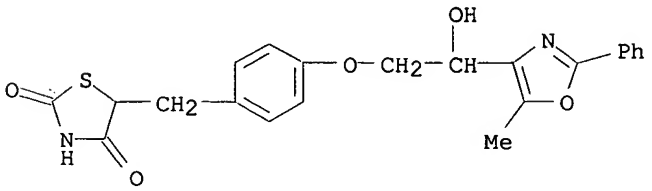
TITLE: Activation of **peroxisome proliferator-activated receptor γ** does not inhibit IL-6 or TNF-α responses of macrophages to lipopolysaccharide in vitro or in vivo

AUTHOR(S): Thieringer, Rolf; Fenyk-Melody, Judy E.; Le Grand, Cheryl B.; Shelton, Beverly A.; Detmers, Patricia A.;

Somers, Elizabeth P.; Carbin, Linda; Moller, David E.; Wright, Samuel D.; Berger, Joel
CORPORATE SOURCE: Departments of Endocrinology and Chemical Biology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Immunology (2000), 164(2), 1046-1054
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the potential use of **peroxisome proliferator-activated receptor .gamma.** (**PPARγ**) agonists as anti-inflammatory agents in cell-based assays and in a mouse model of endotoxemia. Human peripheral blood monocytes were treated with LPS or PMA and a variety of **PPARγ** agonists. Although 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) at micromolar concns. inhibited the production of TNF-α and IL-6, 4 other high affinity **PPAR.gamma.** ligands failed to affect cytokine production Similar results were obtained when the monocytes were allowed to differentiate in culture into macrophages that expressed higher levels of **PPAR.gamma.** or when the murine macrophage cell line RAW 264.7 was used. Furthermore, saturating concns. of a potent **PPARγ** ligand not only failed to block cytokine production, but also were unable to block the inhibitory activity of 15d-PGJ2. Thus, activation of **PPARγ** does not appear to inhibit the production of cytokines by either monocytes or macrophages, and the inhibitory effect observed with 15d-PGJ2 is most likely mediated by a **PPAR.gamma.**-independent mechanism. To examine the anti-inflammatory activity of **PPARγ** agonists in vivo, db/db mice were treated with a potent thiazolidinedione that lowered their elevated blood glucose and triglyceride levels as expected. When thiazolidinedione-treated mice were challenged with LPS, they displayed no suppression of cytokine production Rather, their blood levels of TNF-α and IL-6 were elevated beyond the levels observed in control db/db mice challenged with LPS. Comparable results were obtained with the corresponding lean mice. Thus, compds. capable of activating **PPARγ** in leukocytes will not be useful for the treatment of acute inflammation.

IT **103788-05-2**, AD5075
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**peroxisome proliferator-activated receptor γ** activation by agonists does not inhibit interleukin-6 or **tumor** necrosis factor α responses of macrophages to lipopolysaccharide)

RN 103788-05-2 HCAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:778252 HCAPLUS
DOCUMENT NUMBER: 132:87867

TITLE: A new ligand for the **peroxisome proliferator-activated receptor-γ (PPAR-. gamma.)**, GW7845, inhibits rat mammary carcinogenesis

AUTHOR(S): Suh, Nanjoo; Wang, Yongping; Williams, Charlotte R.; Risingsong, Renee; Gilmer, Tona; Willson, Timothy M.; Sporn, Michael B.

CORPORATE SOURCE: Department of Pharmacology and Norris Cotton Cancer Center, Dartmouth Medical School, Hanover, NH, 03755, USA

SOURCE: Cancer Research (1999), 59(22), 5671-5673
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

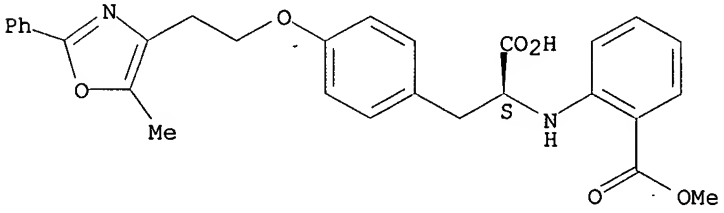
AB We have tested a new ligand for **PPAR-γ** receptor, GW7845, as an inhibitor of exptl. mammary carcinogenesis, using the classic rat model with nitrosomethylurea as carcinogen. Rats were first treated with a single dose of nitrosomethylurea (50 mg/kg body weight, i.p.). Starting 1 wk later, they were fed GW7845, at either 60 or 30 mg/kg of diet, for 2 mo. This agent significantly reduced tumor incidence, tumor number, and tumor weight at both doses. This is the first report of the use of a ligand for **peroxisome proliferator-activated receptor-γ** to prevent exptl. breast cancer.

IT **196809-22-0**, GW 7845
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ligand for **PPAR-γ** receptor, GW7845, for prevention of breast **cancer**)

RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L5 STR
L8 STR
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L51 STR
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L59        2611 SEA FILE=REGISTRY SSS FUL L30 AND (L8 OR L9 OR L10)
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L61         364 SEA FILE=REGISTRY SSS FUL L42 AND (L8 OR L9 OR L10)
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L63         969 SEA FILE=REGISTRY SSS FUL L51 AND (L8 OR L9 OR L10)
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L69        5023 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (PEROXISOME(W)PROLIFER?(W)ACTI
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L70         235 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L68 OR L69) AND L65
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                OR ?TUMOR? OR ?LEUKEM?)
L72          14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L71 AND L70
L81         698 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L65 AND (BENZOIC? OR NICOTINI?
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L82          67 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L81 AND L71
L83          17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L82 AND PENTA?
L84          31 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L83 OR L72
L85           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L84 AND PD=<DECEMBER 31, 1996

L86           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L84 NOT (2005 OR 2004 OR 2003
                OR 2002 OR 2001 OR 2000 OR 1999 OR 1998 OR 1997)/PY
L87           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L85 OR L86


=> d ibib abs hitstr l87 1

L87  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1964:12243  HCAPLUS
DOCUMENT NUMBER:          60:12243
ORIGINAL REFERENCE NO.:   60:2198b-e
TITLE:                    Relation between chemical structure and antitumor
                          action of alkylating compounds
AUTHOR(S):                Berlin, A. Ya.
SOURCE:                   Tr. Inst. Eksperim. i Klinich. Onkol., Akad. Med. Nauk
                          SSSR (1960), 2, 15-28
DOCUMENT TYPE:            Journal
LANGUAGE:                 Unavailable
AB   A discussion is presented of the relation between the hydrolysis rate and
     antitumor action of compds. of the type  4-RC6H4N-(CH2CH2Cl)2, where R is
     COOH, CH2COOH, CH2CH2COOH, CH2CH2CH2COOH, CH2CH2CH2CH2COOH, OCH2COOH,
     OCH2CH2COOH, OCH2CH2CH2COOH, or OCH2CH2CH2CH2-COOH and compds. of the type
     MeSO2O(CH2)nOSO2Me, where n is 2, 3, 4, 5, 6, 7, 8, 9, or 10, and aromatic
     chloroethyl amines 2-MeOC6II4N(CH2CH2Cl)2, 4-MeOC6H4N(CH2CH2Cl)2,
     PhN(CH2CH2Cl)2, and PhN(Et)CH2CH2Cl.  For characterizing antitumor action
     the value "molar activity" is proposed, expressed by the formula Am =
     100T.M/D, where T is the % inhibition of tumors, M is the mol. weight of the
     preparation, and D is the dose in mg./kg. at a daily injection for 15-21 days.
     Values are given for Am for Sarcoma 45 and Ehrlich's tumor for:
     sarcolysine (I), I derivs. of the type 4-(ClCH2)2NC6H4CH2C(NHR)-COOH,
     where R is CHO or Ac, and I derivs. of the type 4-(Cl-
     CH2CH2)2NC6H4CH2CH(NH2)COOR.HCl, where R is Et, iso-Pr, or Bu;
     2,5-disubstituted 6-ethyleniminobenzoquinones, where the 2- and
     5-substituents are, resp.: H and H; Cl and H;  Cl and Cl; EtO and EtO; PrO
     and PrO; derivs. of pyrimidine, where 2,6,5,4-substituents are, resp.: OH,
     Me, (ClCH2CH2)2N, OH; Cl, Me, (ClCH2CH2)2N, Cl; ethylenimino, Me, NO2,
     ethylenimino; OH, Me, [CH2CH2N]P(:O)CH2, OH; ethylenimino, Cl, H,
```
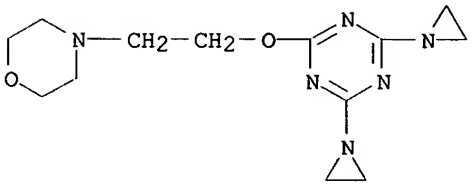

ethylenimino; derivs. of 2,6-bis(ethylenimino)triazines where the 4-substituent is: ethylenimino, NH2, MeNH, PhCH2NH, piperidino, morpholino, β-piperidinoethylamino, β-morpholinoethylamino, MeO, PhCH2O, Et2NCH2CH2O, β-piperidinoethoxy, or β-morpholinoethoxy. From Reference Zh., Biol. Khim. 1963, Abstract Number 14F1308.

IT **72239-63-5**, s-Triazine, 2,4-bis(1-aziridinyl)-6-(2-morpholinoethoxy)-
(**neoplasm** inhibition by)

RN 72239-63-5 HCAPLUS

CN 1,3,5-Triazine, 2,4-bis(1-aziridinyl)-6-[2-(4-morpholinyl)ethoxy]- (9CI) (CA INDEX NAME)



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L61	364	SEA FILE=REGISTRY SSS FUL L42 AND (L8 OR L9 OR L10)
L62	37956	SEA FILE=REGISTRY SSS FUL L46 AND (L8 OR L9 OR L10)
L63	969	SEA FILE=REGISTRY SSS FUL L51 AND (L8 OR L9 OR L10)
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L68	116	SEA FILE=HCAPLUS ABB=ON PLU=ON L66 OR L67
L69	5023	SEA FILE=HCAPLUS ABB=ON PLU=ON (PEROXISOME(W)PROLIFER?(W)ACTIVAT?(5A)RECEPT? OR PPAR)(L)GAMMA
L70	235	SEA FILE=HCAPLUS ABB=ON PLU=ON (L68 OR L69) AND L65
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L72	14	SEA FILE=HCAPLUS ABB=ON PLU=ON L71 AND L70
L81	698	SEA FILE=HCAPLUS ABB=ON PLU=ON L65 AND (BENZOIC? OR NICOTINI?)(2A)ACID
L82	67	SEA FILE=HCAPLUS ABB=ON PLU=ON L81 AND L71
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L84	31	SEA FILE=HCAPLUS ABB=ON PLU=ON L83 OR L72

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L91  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        1996:656494  HCAPLUS
DOCUMENT NUMBER:         126:372
TITLE:                   Structure-activity relationship studies on benzofuran
                         analogs of propafenone-type modulators of tumor cell
                         multidrug resistance
AUTHOR(S):               Ecker, Gerhard; Chiba, Peter; Hitzler, Manuela;
                         Schmid, Diethard; Visser, Klaus; Cordes, Hans Peter;
                         Csoellei, Josef; Seydel, Joachim K.; Schaper,
                         Klaus-Juergen
CORPORATE SOURCE:        Institute of Pharmaceutical Chemistry, University of
                         Vienna, Vienna, A-1090, Austria
SOURCE:                  Journal of Medicinal Chemistry (1996), 39(24),
                         4767-4774
                         CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER:               American Chemical Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   A series of benzofurylethanolamine analogs of propafenone have been prepared
     and evaluated for multidrug resistance-reversing activity in two in vitro
     assay systems.  As for propafenones, an excellent correlation of biol.
     data with calculated lipophilicity values was found for benzofurans, whereby
     the latter generally had lower activity/lipophilicity ratios.  Almost
     identical slopes of the regression lines were obtained for both
     propafenones and benzofurans.  Multiple linear regression anal. of the
     complete data set yielded an equation with excellent predictive power
     (r2cross-valid = 0.968).  Interaction measurements with artificial
     membranes indicated that the differences in activity between these two
     series of compds. are not due to differences in the interaction pattern
     with biol. membranes.
IT   86383-89-3 183014-30-4 183014-34-8
     RL: BAC (Biological activity or effector, except adverse); BPR (Biological
     process); BSU (Biological study, unclassified); PRP (Properties); THU
     (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
        (structure-activity relationship studies on benzofuran analogs of
        propafenone as modulators of tumor cell multidrug
        resistance in relation to lipophilicity and interaction with artificial
        membranes)
RN   86383-89-3  HCAPLUS
CN   1-Propanone, 1-[2-[2-hydroxy-3-(4-morpholinyl)propoxy]phenyl]-3-phenyl-
     (9CI)  (CA INDEX NAME)
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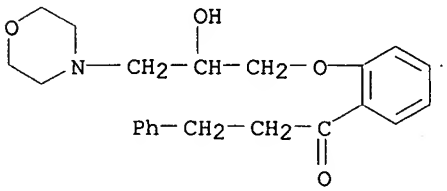
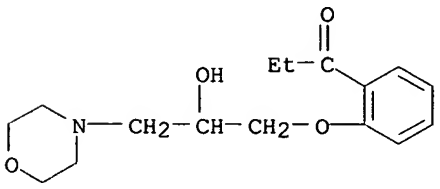
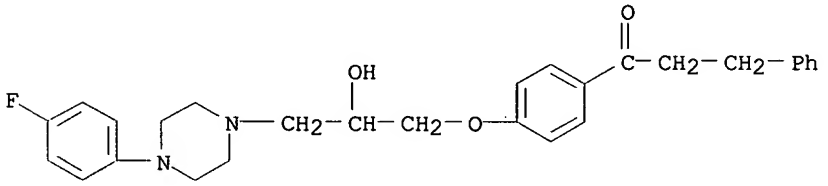


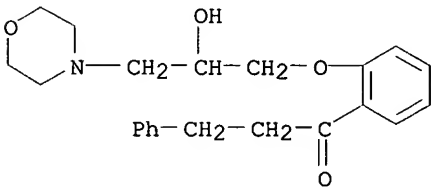
RN 183014-30-4 HCAPLUS
CN 1-Propanone, 1-[2-[2-hydroxy-3-(4-morpholinyl)propoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 183014-34-8 HCAPLUS
CN 1-Propanone, 1-[4-[3-[4-(4-fluorophenyl)-1-piperazinyl]-2-hydroxypropoxy]phenyl]-3-phenyl- (9CI) (CA INDEX NAME)



IT **86383-06-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity relationship studies on benzofuran analogs of propafenone as modulators of **tumor** cell **multidrug** resistance in relation to lipophilicity and interaction with artificial membranes)
RN 86383-06-4 HCAPLUS
CN 1-Propanone, 1-[2-[2-hydroxy-3-(4-morpholinyl)propoxy]phenyl]-3-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

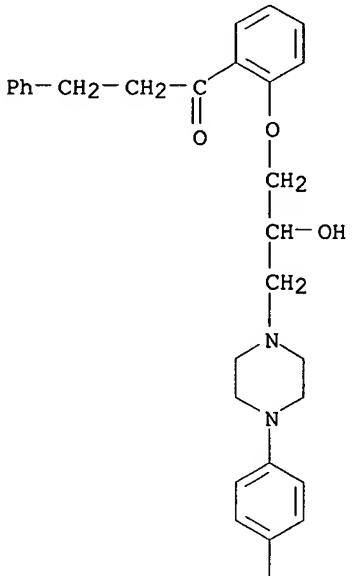


● HCl

IT **163858-57-9 163858-59-1 178691-48-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity relationship studies on benzofuran analogs of propafenone as modulators of **tumor** cell **multidrug** resistance in relation to lipophilicity and interaction with artificial membranes)
RN 163858-57-9 HCAPLUS

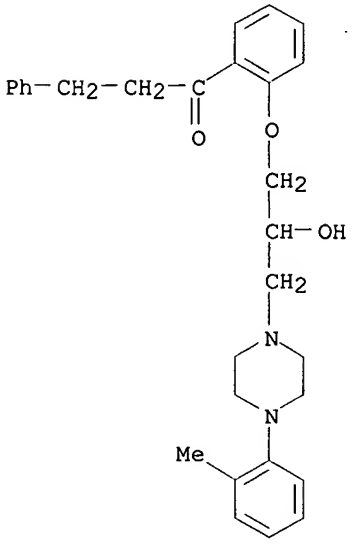
CN 1-Propanone, 1-[2-[2-hydroxy-3-[4-(4-methoxyphenyl)-1-piperazinyl]propoxy]phenyl]-3-phenyl- (9CI) (CA INDEX NAME)

PAGE 1-A

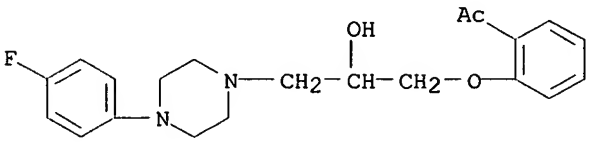


PAGE 2-A

RN 163858-59-1 HCAPLUS
CN 1-Propanone, 1-[2-[2-hydroxy-3-[4-(2-methylphenyl)-1-piperazinyl]propoxy]phenyl]-3-phenyl- (9CI) (CA INDEX NAME)



RN 178691-48-0 HCAPLUS
CN Ethanone, 1-[2-[3-[4-(4-fluorophenyl)-1-piperazinyl]-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

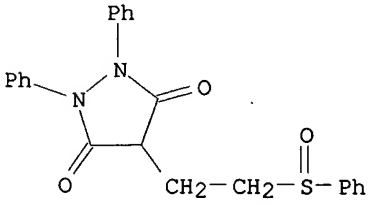


L91 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:200808 HCAPLUS
DOCUMENT NUMBER: 124:278313
TITLE: Transport properties of the multidrug resistance-associated protein (MRP) in human tumor cells
AUTHOR(S): Hollo, Zsolt; Homolya, Laszlo; Heged+dblac;us, Tamas; Sarkadi, Balazs
CORPORATE SOURCE: National Institute of Haematology and Immunology, Daroczi u. 24, Budapest, H-1113, Hung.
SOURCE: FEBS Letters (1996), 383(1,2), 99-104
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this paper we demonstrate that the expression of the multidrug resistance-associated protein (MRP) in a variety of intact human tumor cells results in the ATP-dependent, mutually exclusive extrusion of both the acetoxymethyl ester and the free anion forms of the fluorescent dye calcein, as well as that of a fluorescent pyrenemaleimide-glutathione conjugate. The MRP-dependent transport of all these three model compds. closely correlates with the expression level of MRP and is cross-inhibited by hydrophobic anticancer drugs, by reversing agents for MDR1, and also by compds. not influencing MDR1, such as hydrophobic anions, alkylating agents, and inhibitors of organic anion transporters. Cellular glutathione depletion affects neither the MRP-dependent extrusion of calcein AM or free calcein, nor its modulation by most hydrophobic or anionic compds., although eliminating the cross-inhibitory effect of glutathione conjugates. These results suggest that the outward pumping of both hydrophobic uncharged and water-soluble anionic compds., including glutathione conjugates, is an inherent property of MRP, and offer sensitive methods for the functional diagnostics of this transport protein as well as for the rapid screening of drug-resistance modulating agents.

IT **57-96-5**, Sulfinpyrazone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(transport properties of **multidrug** resistance-associated protein in human **tumor** cells)

RN 57-96-5 HCAPLUS
CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L91 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:872796 HCAPLUS
DOCUMENT NUMBER: 123:329465
TITLE: Relationship between multidrug resistant gene expression and multidrug resistant-reversing effect of MS-209 in various tumor cells
AUTHOR(S): Baba, Makoto; Nakanishi, Osamu; Sato, Wakao; Saito, Akiko; Miyama, Yukio; Yano, Osamu; Shimada, Shizuo; Fukazawa, Nobuyuki; Naito, Mikihiko; Tsuruo, Takashi
CORPORATE SOURCE: Institute Biological Science, Mitsui Pharmaceuticals, Inc., Mobara, 297, Japan
SOURCE: Cancer Chemotherapy and Pharmacology (1995), 36(5), 361-7
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

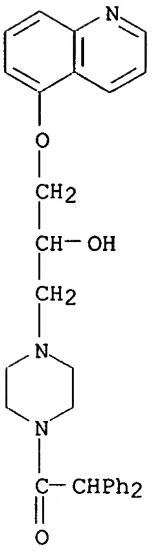
AB MS-209 is a novel quinoline compound which can overcome multidrug resistance (MDR) both in vitro and in vivo, while having a low level of side effects, and is now being evaluated in a clin. phase II study. Reverse transcription-polymerase chain reaction (RT-PCR) was used to quantitate the expression levels of MDR genes in various mouse and human tumor cell lines. The MDR gene and the β actin gene, as the internal reference standard, were coamplified sep., and the relative expression of the MDR gene was represented by the MDR/β actin ratio. The in vitro MDR-reversing effect of MS-209 was then compared with the MDR gene expression (MDR/β actin ratio). The authors found a significant correlation between these two parameters. Moreover, a significant correlation was also observed between the level of expression of the MDR1 gene and that of P-glycoprotein in human cell lines. Therefore, the efficacy of MS-209 seems to specifically depend on the level of MDR gene expression (P-glycoprotein). From these observations, it is suggested that RT-PCR assays of MDR1 gene in tumor biopsy specimens might be an effective means to predict the response of tumor cells to combination therapy with MS-209.

IT **158681-49-3**, MS-209
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(relationship between **multidrug** resistant gene expression and **multidrug** resistant-reversing effect of MS-209 in various **tumor** cells in relation to combination **therapy** in human and laboratory animal cells)

RN 158681-49-3 HCAPLUS
CN 1-Piperazineethanol, 4-(diphenylacetyl)-α-[(5-quinolinyloxy)methyl]-, (2E)-2-butenedioate (2:3) (salt) (9CI) (CA INDEX NAME)

CM 1

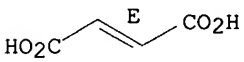
CRN 129716-58-1
CMF C30 H31 N3 O3



CM 2

CRN 110-17-8
CMF C4 H4 O4

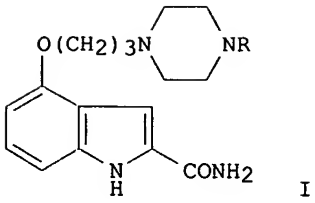
Double bond geometry as shown.



L91 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:761990 HCAPLUS
DOCUMENT NUMBER: 123:286095
TITLE: Amines to sensitize multidrug-resistant cells
INVENTOR(S): Abraham, Irene; Hester, Jackson B., Jr.
PATENT ASSIGNEE(S): Upjohn Co., USA
SOURCE: U.S., 20 pp. Cont.-in-part of U.S. Ser. No. 682,809, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5436337	A	19950725	US 1993-132515	19931006
PRIORITY APPLN. INFO.:			US 1993-132515	B2 19931006
			US 1991-682809	19910409

GI



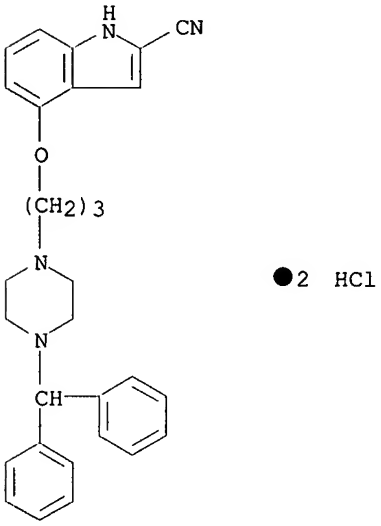
I

AB The piperazines I [R = CHPh2, 2,4-dipyrrolidino-6-pyrimidinyl] were prepared for use as sensitizers for anticancer therapy. Thus, 4-benzyloxyindole-2-carboxylic acid was amidated, debenzylated, and alkylated to give I [R = CHPh2], which was dehydrated to the nitrile (II). II was combined with adriamycin to treat drug-resistant pancreatic carcinoma. Steroidal amines, alkylamines, bicyclic amines, bicyclic ethers, and naphthoxazines are also useful in treating individuals who have cancer that has become resistant to cancer chemotherapeutic agents and in preventing the resistance from developing or slowing the rate of resistance to the chemotherapeutic agents.

IT **145521-35-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(piperazinopropoxyindolecarboxamides in preparation of **anticancer drug** sensitizers)

RN 145521-35-3 HCAPLUS

CN 1H-Indole-2-carbonitrile, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]-, dihydrochloride (9CI) (CA INDEX NAME)



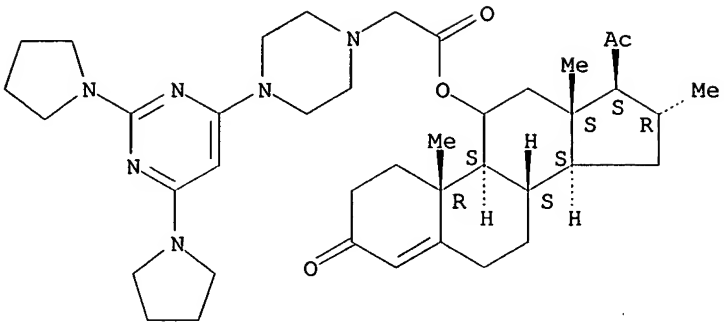
●2 HCl

IT **145033-49-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(piperazinopropoxyindolecarboxamides in preparation of **anticancer drug** sensitizers)

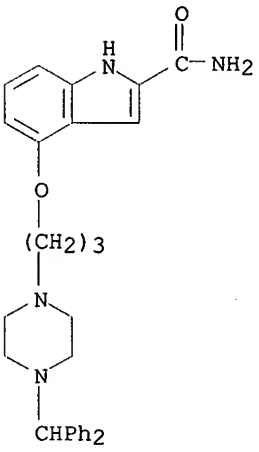
RN 145033-49-4 HCAPLUS

CN Pregn-4-ene-3,20-dione, 11-[[[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]acetyl]oxy]-16-methyl-, (16α)- (9CI) (CA INDEX NAME)

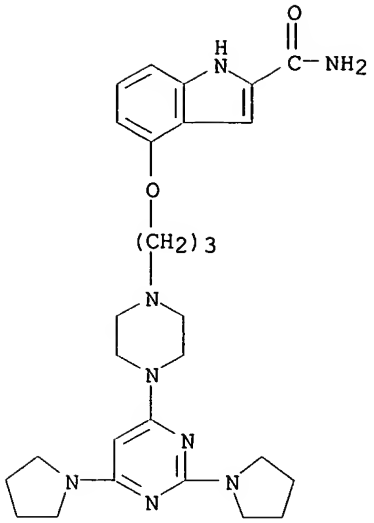
Absolute stereochemistry.



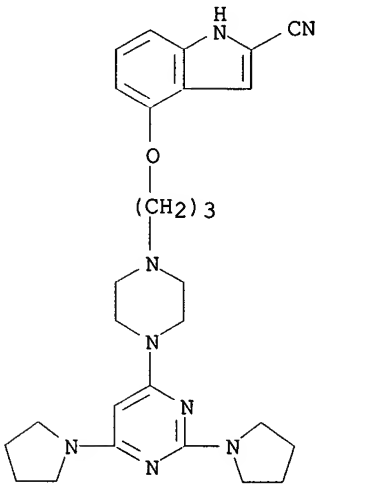
IT **145014-50-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(piperazinopropoxyindolecarboxamides in preparation of **anticancer drug** sensitizers)
RN 145014-50-2 HCAPLUS
CN 1H-Indole-2-carboxamide, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



IT **145014-51-3P 145014-53-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(piperazinopropoxyindolecarboxamides in preparation of **anticancer drug** sensitizers)
RN 145014-51-3 HCAPLUS
CN 1H-Indole-2-carboxamide, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



RN 145014-53-5 HCAPLUS
CN 1H-Indole-2-carbonitrile, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



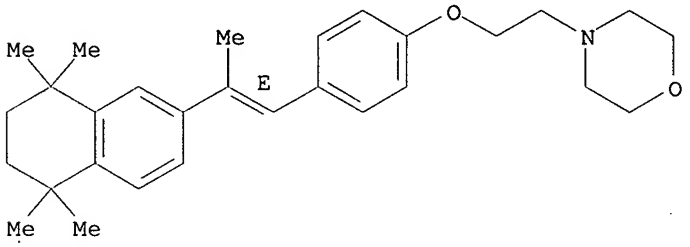
L91 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:87624 HCAPLUS
DOCUMENT NUMBER: 122:426
TITLE: The arotinoid Ro 40-8757 has antiproliferative effects in drug-resistant human colon and breast cancer cell lines in vitro
AUTHOR(S): Louvet, Christophe; Empereur, Sylvie; Fagot, Dominique; Forgue-Lafitte, Elisabeth; Chastre, Eric; Zimber, Amazia; Mester, Jan; Gespach, Christian
CORPORATE SOURCE: INSERM U55, Paris, 75012, Fr.
SOURCE: Cancer Letters (Shannon, Ireland) (1994), 85(1), 83-6
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have examined the antiproliferative effects of the arotinoid Ro 40-8757

in 3 drug-resistant human adenocarcinoma cell lines: the colonic cells HT29-5FU and CaCo2, and the mammary cells MCF-7mdr1. Whereas all-trans retinoic acid had no effect at the concentration of 10-6 M, Ro 40-8757 was found to exert a high antiproliferative action with similar inhibitory potency (IC50) in drug-resistant and parental cell lines (range, 0.06 + 10-6 to 0.57+10-6 M). We conclude that: (1) thymidylate synthase is not involved in the mechanism of action of Ro 40-8757; (2) the mdr1 gene product does not recognize this retinoic derivative; and (3) Ro 40-8757, alone or in combinations with other cytotoxic drugs, can be very useful in patients with progressive disease after conventional chemotherapy.

IT **125533-88-2**, Ro 40-8757
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arotinoid Ro 40-8757 has antiproliferative effects in **drug**-resistant human colon and breast **cancer** cell lines in vitro)

RN 125533-88-2 HCAPLUS
CN Morpholine, 4-[2-[4-[(1E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]phenoxy]ethyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L91 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:52416 HCAPLUS
DOCUMENT NUMBER: 118:52416
TITLE: Use of amines to sensitize multidrug-resistant cells
INVENTOR(S): Abraham, Irene; Hester, Jackson Boling
PATENT ASSIGNEE(S): Upjohn Co., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9218089	A2	19921029	WO 1992-US2237	19920327
WO 9218089	A3	19930304		
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
AU 9217738	A1	19921117	AU 1992-17738	19920327
EP 579754	A1	19940126	EP 1992-910802	19920327
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				

PRIORITY APPLN. INFO.: US 1991-682809 A2 19910409
WO 1992-US2237 A 19920327

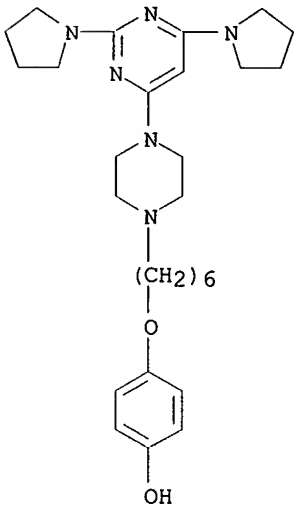
OTHER SOURCE(S): MARPAT 118:52416

AB Multidrug resistance to cancer therapeutic agents in human cancer patients is treated by administering a sensitizing agent comprising a steroidal, aliphatic, or bicyclic amine, a bicyclic or tricyclic ether, or an indole derivative (Markush structures given). Thus, in a patient with pancreatic carcinoma treated with Adriamycin, the development of Adriamycin

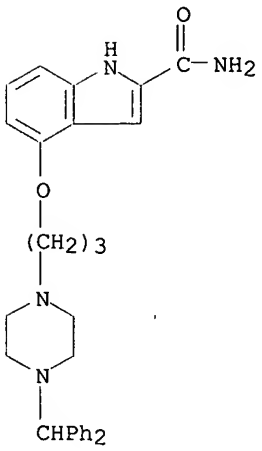
resistance was reversed by treatment with 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]indole-2-carboxamide (I) (0.01-5.0 mg/kg/h over 5 days). I was prepared by amidation of 4-(benzyloxy)indole-2-carboxylic acid, catalytic hydrogenation, and condensation of the product 4-hydroxyindole-2-carboxamide with 1-chloro-3-[4-(diphenylmethyl)-1-piperazinylpropane.

IT **122004-37-9 145014-50-2 145014-51-3**
145014-52-4 145014-53-5 145033-49-4
RL: BIOL (Biological study)
(**multidrug** resistance to **neoplasm** inhibitors reversal by)

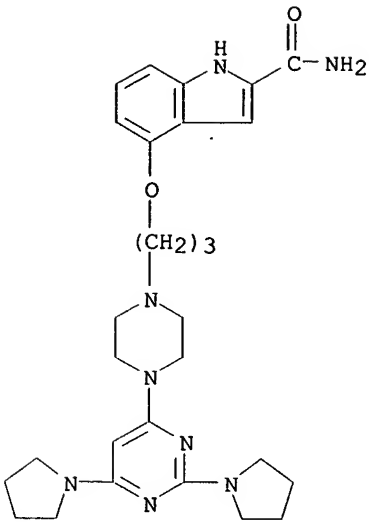
RN 122004-37-9 HCAPLUS
CN Phenol, 4-[[6-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]hexyl]oxy]- (9CI) (CA INDEX NAME)



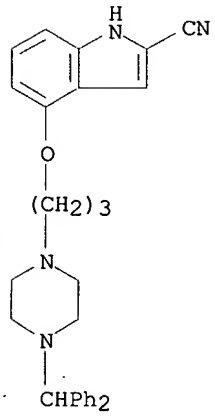
RN 145014-50-2 HCAPLUS
CN 1H-Indole-2-carboxamide, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



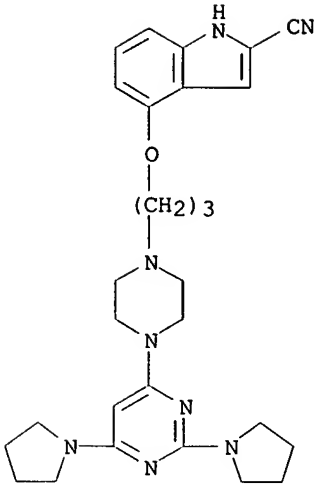
RN 145014-51-3 HCAPLUS
CN 1H-Indole-2-carboxamide, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



RN 145014-52-4 HCAPLUS
CN 1H-Indole-2-carbonitrile, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)

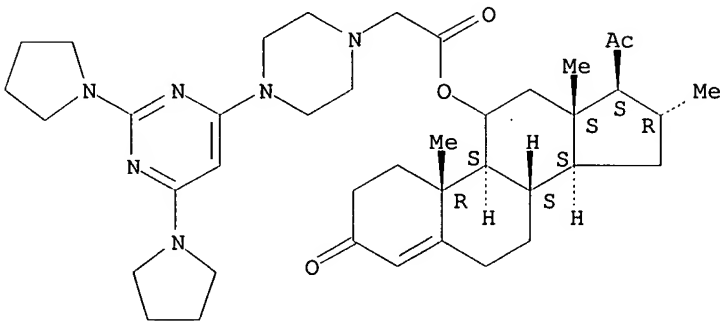


RN 145014-53-5 HCAPLUS
CN 1H-Indole-2-carbonitrile, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)

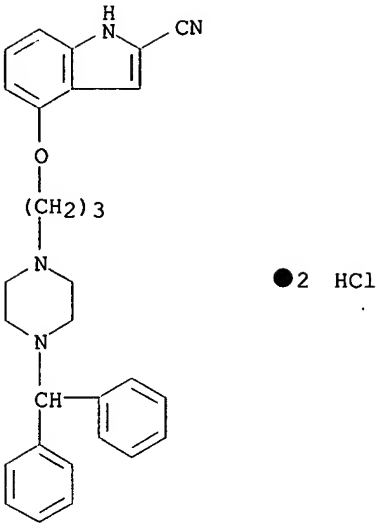


RN 145033-49-4 HCAPLUS
CN Pregn-4-ene-3,20-dione, 11-[[[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]acetyl]oxy]-16-methyl-, (16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **145521-35-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for reversal of **multidrug** resistance to **neoplasm** inhibitors)
RN 145521-35-3 HCAPLUS
CN 1H-Indole-2-carbonitrile, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L91 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:463950 HCAPLUS
DOCUMENT NUMBER: 111:63950
TITLE: Topical pharmaceuticals containing triamcinolon acetonide-21-oic acid methyl ester for the prevention of UV radiation-induced carcinogenic responses of the skin
INVENTOR(S): Ross, Peter M.; Bradlow, Leon H.
PATENT ASSIGNEE(S): Rockefeller University, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8807371	A2	19881006	WO 1988-US1036	19880325
WO 8807371	A3	19881201		
W: AU, JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8817077	A1	19881102	AU 1988-17077	19880325
AU 613370	B2	19910801		
EP 307468	A1	19890322	EP 1988-904039	19880325
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
CA 1316827	A1	19930427	CA 1988-562419	19880325
PRIORITY APPLN. INFO.:			US 1987-30764 A	19870325
			US 1988-161542 A	19880229
			WO 1988-US1036 A	19880325

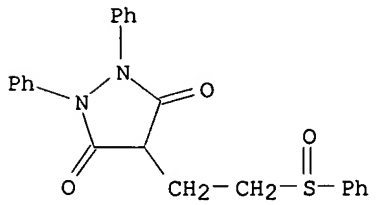
AB Topical formulations containing triamcinolone acetonide-21-oic acid Me ester (I), and, optionally, other compds., which inhibit prostaglandin biosynthesis through the arachidonic acid cascade, useful in the treatment of UV-exposed skin to inhibit UV radiation suppression of delayed hypersensitivity in the epidermis thereby reducing or obviating the carcinogenic effects of sunburn, are prepared A cream formulation contained I 0.5, cetyl esters wax 20.0, cetyl stearyl alc. 100.0, sorbitan monostearate 25.0, polysorbitan 60 20.0, cetyl dodecanol 100.0, propylene glycol 100.0, benzyl alc. 10.0 mg/g cream, and H2O q.s. 1 g. The shaven lower backs of mice were exposed to 254 nm light at an incident dose of 12 W/cm2 for 30-40 min (254 nm light penetrates the epidermis less deeply

than UV light) and immediately following the irradiation treated with triamcinoline acetonide-21-oic acid methyl ester. This active agent had no effect on unirradiated skin but enhanced neutrophilic infiltration and epidermal hyperplasia in UV-irradiated skin. Alternatively, a method for the prevention of UV-induced carcinogenic effects comprises the administration of compds. affecting the arachidonic acid cascade or prostaglandin synthesis; such compds. are aspirin, ibuprofen, indomethacin, salicylic acid, phenylbutazone, sulfinpyrazon, and sulindac (no data).

IT **57-96-5**, Sulfinpyrazon
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pharmaceuticals** containing, for prevention of UV-induced skin **cancer**)

RN 57-96-5 HCAPLUS

CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L91 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1986:61741 HCAPLUS

DOCUMENT NUMBER: 104:61741

TITLE: Mutagenicity and metabolic cooperation inhibition tests of cilostazol

AUTHOR(S): Shibahara, Toshikazu; Awogi, Takumi; Kaneko, Etsuko; Itoh, Toshiaki; Fukazawa, Yoko; Ishii, Kiyoshi; Tsushimoto, Gen

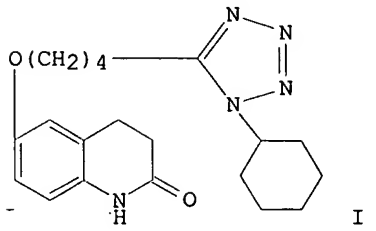
CORPORATE SOURCE: Tokushima Res. Inst., Otsuka Pharm. Co., Ltd., Tokushima, 771-01, Japan

SOURCE: Iyakuhin Kenkyu (1985), 16(5), 1093-9
CODEN: IYKEDH; ISSN: 0287-0894

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

GI

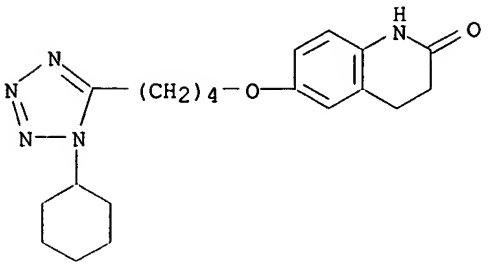


I

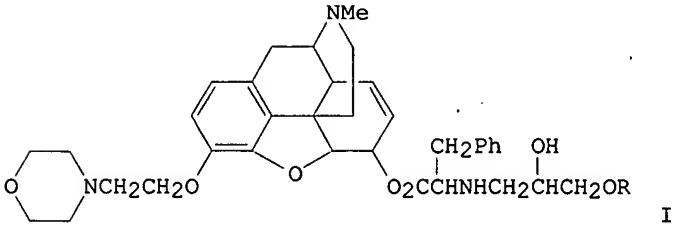
AB The antithrombotic **drug** cilostazol (I) [**73963-72-1**] was devoid of both mutagenicity (as measured by standard DNA-repair and reverse-mutation tests in bacteria) and of **tumor**-promoting activity (as measured by inhibition of metabolic cooperation between cultured Chinese hamster cells).

IT **73963-72-1**
RL: BIOL (Biological study)
(mutagenicity of and **neoplasm** promotion by)

RN 73963-72-1 HCAPLUS
CN 2(1H)-Quinolinone, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro- (9CI) (CA INDEX NAME)



L91 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:221738 HCAPLUS
DOCUMENT NUMBER: 98:221738
TITLE: Fixation of drugs on cellulose releasable by enzymes
AUTHOR(S): Lapicque, Francoise; Dellacherie, Edith
CORPORATE SOURCE: Lab. Chim. Phys. Macromol., ENSIC, Nancy, 54042, Fr.
SOURCE: Makromolekulare Chemie (1983), 184(2), 277-85
CODEN: MACEAK; ISSN: 0025-116X
DOCUMENT TYPE: Journal
LANGUAGE: French
GI



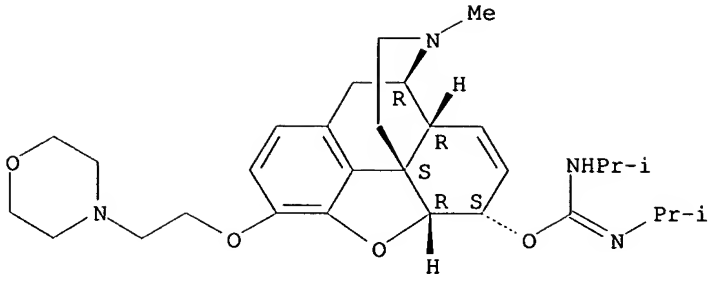
I

AB As an approach to the programmed release of **drugs** a polymeric carrier (I; R = cellulose) from which the **drug** would be released by degradation of definite covalent chemical bonds by means of specific enzymes, pholcodine (II) [**509-67-1**], an **antitumor drug**, was coupled with an insol. physiol. inert polymer, cellulose [9004-34-6], using L-phenylalanine [63-91-2] as a spacer arm. An ester function was chosen linking the hydroxyl group of II and the carboxylic group of L-phenylalanine as the chemical bond between **drug** and amino acid. This linkage was not hydrolyzed in simulated digestive fluids containing pepsin or trypsin; it was only broken in the presence of α-chymotrypsin to slowly release the parent **drug**.

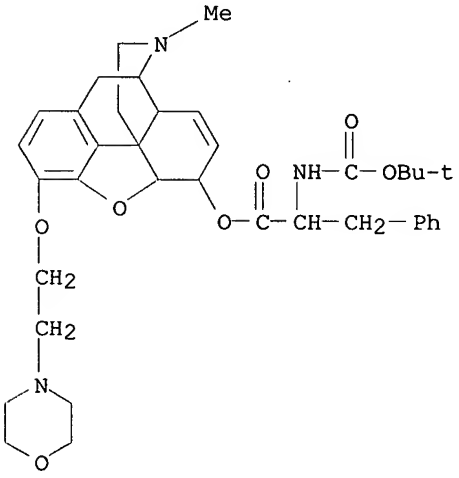
IT **85369-02-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with phenylalanine)

RN 85369-02-4 HCAPLUS
CN Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]-, N,N'-bis(1-methylethyl)carbamimidate (ester), (5α,6α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

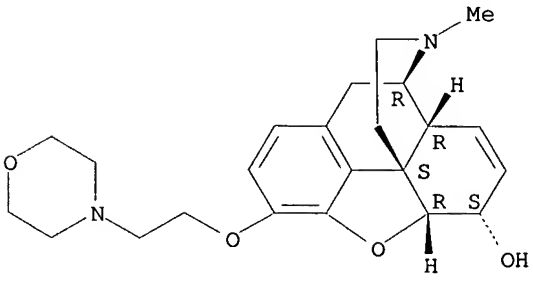


IT **85369-03-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 85369-03-5 HCAPLUS
CN L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-, (5α,6α)-7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]morphinan-6-yl ester (9CI) (CA INDEX NAME)



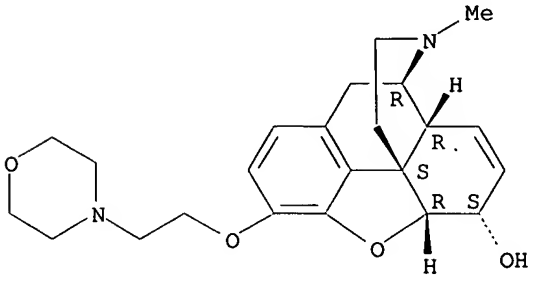
IT **509-67-1DP**, reaction products with cellulose and phenylalanine
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for **drug** release by enzyme cleavage)
RN 509-67-1 HCAPLUS
CN Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]-, (5α,6α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

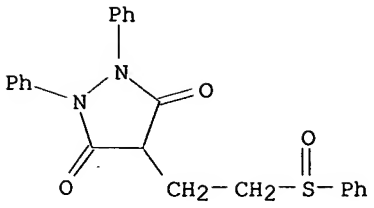


IT **509-67-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with diisopropylcarbodiimide, isourea derivative from)
RN 509-67-1 HCAPLUS
CN Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]-, (5α,6α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



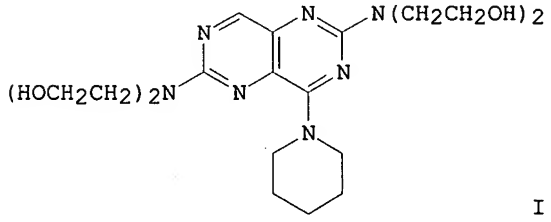
L91 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:449486 HCAPLUS
DOCUMENT NUMBER: 97:49486
TITLE: Interruption of tumor-associated platelet consumption with platelet enzyme inhibitors
AUTHOR(S): Slichter, Sherrill J.; Weiden, Paul L.; O'Donnell, Margaret R.; Storb, Rainer
CORPORATE SOURCE: Sch. Med., Univ. Washington, Seattle, WA, 98104, USA
SOURCE: Blood (1982), 59(6), 1252-8
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Twenty dogs with naturally occurring metastatic **tumors** were treated with anticoagulants (Warfarin [81-81-2]) or platelet enzyme inhibitor **drugs** (dipyridamole [58-32-2], dipyridamole plus aspirin [50-78-2], RA233 [13665-88-8], sulfinpyrazone [**57-96-5**], or a combination of RA233 and sulfinpyrazone) to determine if **tumor**-related redns. in platelet survival and concentration could be reversed. Anticoagulation was ineffective, while platelet enzyme inhibitors were able to produce improvements in platelet survival. Of the 18 dogs with metastatic **tumor** treated with platelet enzyme inhibitors, only 5 (28%) showed a reduction in platelet survival during the first week of observation on **therapy** compared to their baseline survivals. This is significantly different than the decreases in platelet survivals observed in 8 of 10 untreated dogs (80%) with metastatic **tumor** observed for the same interval. Furthermore, 8 of the 18 treated dogs (44%) had platelet survivals within 2 standard deviations of normal, compared to only 1 of 10 untreated dogs. Of the 8 dogs with normal platelet survivals, 6 were treated with a combination of a phosphodiesterase inhibitor (RA233 or dipyridamole) and a cyclooxygenase inhibitor (sulfinpyrazone or aspirin). The combination of RA233 and sulfinpyrazone was the best **drug** program tested and resulted in normal platelet survivals in 63% and improved platelet counts in 75% of the animals treated. Thus, platelet enzyme inhibitors with different mechanisms of action may have a synergistic effect in reversing the abnormal platelet hemostasis found in a variety of spontaneously occurring canine **neoplasms**.
IT **57-96-5**
RL: BIOL (Biological study)
(platelet survival inhibition by **tumor** response to RA233 and)
RN 57-96-5 HCAPLUS
CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L91 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1981:52940 HCAPLUS
DOCUMENT NUMBER: 94:52940
TITLE: Antithrombotic pharmaceutical combination
INVENTOR(S): Slichter, Sherrill J.
PATENT ASSIGNEE(S): Thomae, Dr. Karl, G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2904736	A1	19800828	DE 1979-2904736	19790208
US 4285945	A	19810825	US 1979-76510	19790917
EP 14392	A1	19800820	EP 1980-100385	19800125
EP 14392	B1	19811104		
R: BE, CH, DE, FR, GB, IT, LU, NL, SE				
JP 55105618	A2	19800813	JP 1980-14258	19800207
AU 8055311	A1	19800814	AU 1980-55311	19800207
AU 533693	B2	19831208		
ZA 8000715	A	19811028	ZA 1980-715	19800207
IL 59335	A1	19830331	IL 1980-59335	19800207

PRIORITY APPLN. INFO.: DE 1979-2904736 A 19790208
GI



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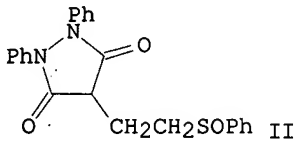
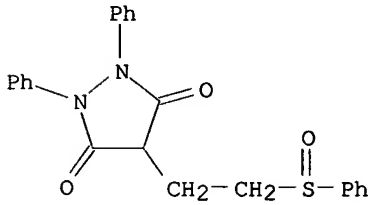


II

AB A combination of I [13665-88-8] and sulfinpyrazone (II) [**57-96-5**] in a ratio of 10:1 to 1:10 is formulated in a sugar-coated tablet and capsule form for oral administration as an antithrombotic agent, the 2 components having a synergistic action in this respect. Thus, 50.0 mg I and 50.0 mg II were formulated into tablets. When dogs with malignant **tumors** were given the combination of I and II in a ratio of 1:1 or 1:2 in a dose of 50-100 mg/kg, the thrombocyte survival time in the body increased from .apprx.2 days to the near normal values of 4.5-4.8 days. The increase in the thrombocyte survival time (as measured with labeled cells) indicates a decreased tendency for thrombosis. The doses suggested for humans are 25-100 mg I and 50-175 mg II 2-4 times daily, and these are well below the LD50 levels.

IT **57-96-5**
RL: BIOL (Biological study)
(antithrombotic **pharmaceutical** synergistic combination with piperidinopyrimidine derivative)
RN 57-96-5 HCAPLUS
CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



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